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Novel treatment approaches and future directions in substance use disorders

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Novel treatment approaches and future directions in substance use disorders

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ORIGINAL RESEARCH
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Comparing the Effects of Melatonin and Zolpidem on Mental Health and Sexual Function in Men With Opioid Addiction: Evidence From a Randomized Clinical Trial

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Background: Mental health problems and impaired sexual function are widely reported among those suffering from drug abuse, particularly among those under methadone maintenance therapy (MMT).

Aims: The current study aimed to, firstly, investigate the effect of melatonin and zolpidem on mental health and sexual function of those with drug abuse under MMT, and, secondly, to compare the effects of melatonin and zolpidem on the studied outcomes.

Methods: The current randomized, single-blind, placebo-controlled clinical trial was conducted on 98 participants who were randomly assigned into three groups of melatonin ($n = 34$), zolpidem ($n = 32$), and placebo ($n = 32$). All participants received the intervention once a day for 30 days, without changes in nutrition. Mental health and sexual function were measured before and 30 days after the intervention.

Results: The mean age of participants in the groups of melatonin, zolpidem, and placebo was 35.8 ± 9.6 years (22–58 years of old), 35.9 ± 9.3 years (21–58), and 37.2 ± 7.8 years (26–53), respectively. Sexual function mean score was significantly increased from 38 to 41 in the melatonin group, while it deceased in zolpidem (from 39.1 to 38) and placebo (39.25–38.59) groups. Also, mental health mean scores improved statistically significantly in the melatonin group (from 60.65 to 43.56; $p = 0.002$), and descriptively in the zolpidem group (57.88–51.18; $p = 0.129$). Concerning both outcomes, the observed improvement was considerably higher in the melatonin group. The highest improvement was observed in dimensions of overall satisfaction and depression in the melatonin group (1.18 and −8.4, respectively).

Conclusion: Melatonin could significantly improve both mental health and some domains of sexual function of those with drug abuse under MMT, while zolpidem did not show a significant effect.

Trial Registration Number: https://www.irct.ir/trial/53047, identifier: IRCT20201214049718N1.

Keywords: melatonin, zolpidem, sexual function, mental health, methadone maintenance therapy

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INTRODUCTION

In today's modern world, inclination toward opioid addiction is on the rise, due to several reasons such as stress from working long hours, high costs of living, etc. (1–3), not to mention the effects of the Covid-19 pandemic (4). The United Nations reported that about 275 million people used opioid combination products worldwide in 2020, with a growth rate of 22% from 2010 (5). In addition, there are evidence indicating that mental health disorders and opioid addiction co-exist in most cases, as in response to mental problems some will try to address them with opioid combination products (6, 7). So that nearly 50% of those who suffer from mental disorders are affected by opioid addiction (8). In addition, opioid addiction may magnify many mental health problems (9), which in turn enhances inclination toward more addiction (10, 11). Also, one of the most common complaints of those who are trying to quit opioid addiction is mental health problems (12, 13). Furthermore, methadone maintenance therapy (MMT), which is widely used to treat opioid addiction by preventing opioid withdrawal and reducing cravings, is associated with increased risk of worsened mental health problems (14). It is worth noting that addicted persons suffering from psychological health problems are at increased risk of having lower quality of life (QoL) (15), which in turn translates into higher mortality rates (14).

Furthermore, those with opioid addiction also suffer from impaired sexual function (16). While such dysfunctions may occur in any stage of the normal sexual cycle, erectile dysfunction (ED) or impaired orgasm function are among the earliest issues (17), which cause an extra burden, with long-term consequences, on their mental health problems, apart from the dissatisfaction of their partners. Therefore, evaluating the mental health and sexual function of those who suffer from opioid addiction can provide valuable information about how to address their problems more efficiently, which in turn paves the way for better and faster quit.

Currently, several types of interventions are available for this purpose, including pharmacological, behavioral, cognitive, and hormonal. Pharmacological interventions (e.g., benzodiazepine, bupropion, trazodone) are one of the most efficient interventions with immediate effects; however, caution should be taken as often lead to addiction or cause side effects, which results in more declines in the QoL (18). Herbal medicines such as Ginseng and Rosa Damascena Oil have also been studied, but drug interactions, the time required for effectiveness, and the acceptance of patients in the use of herbal medicines should be considered (19, 20). While the impacts of other interventions would be observable in the long term. There are extensive evidence regarding the potential effects of melatonin on reducing inclination toward opioid addiction and relapse of addiction, as well as regulation of mental health mechanisms (21). In addition, melatonin is associated with improved mental health, through alleviating lipopolysaccharide-induced anxiety, which indicates its therapeutic effect (22, 23). The pineal gland secrets melatonin, and its secretion decreases during periods of depression, which is another reason to support its unique role in mental health regulation. In addition, zolpidem is one of the most effective non-benzodiazepine medications available to treat mental health issues, mainly through activating GABA receptors, which in turn opens chloride channels, declines the firing rate of neurons and muscle fibers, and selectively binds to the subunit-specific GABA receptors (24).

In this study, we sought to use a drug in addition to methadone that could address common patient problems such as mental and sexual problems. Usually, people on methadone treatment suffer from these problems and increase the dose of their methadone drug to solve it. We were looking for a drug that we could use to manage several common complaints of these patients. To the best of our knowledge, few studies have simultaneously investigated the effects of melatonin and zolpidem supplementation on mental health and sexual function of those under MMT. "We expected melatonin to be more effective than zolpidem and placebo." Based on what was mentioned before, the purpose of this article is to, firstly, investigate the effect of melatonin and zolpidem on depression, anxiety and stress dimensions of mental health and erectile function aspect of sexual function of those under MMT, and, secondly, to compare the effects of melatonin and zolpidem on the studied outcomes.

METHODS

Study Design and Participants

The current randomized, single-blinded, placebo-controlled clinical trial is carried out on males receiving outpatient treatment for opioid addiction in the city of Isfahan, Iran in 2021. Participants were selected from a single center. All eligible participants were followed up for 1 month (from April 3, 2021, to May 22, 2021), and to prevent contamination, they were asked to refer on particular days.

The sample size was estimated as 32 subjects per group, following the study by (16, 21) with a 95% confidence interval and 80% statistical test power, using the following formula:

$$n = 2^{*}(z\_(1-\alpha/2) + z\_(1-\beta))2\times sd2)/d2$$

However, allowing for a 10% dropout, the estimated sample size per group was increased to 35. Consequently, a total of 105 subjects with opioid addiction under the MMT with sleep quality of at least 5 were selected using convenience sampling. Then, using the Excel software they were divided into three groups of melatonin, zolpidem, and placebo. Those with the following criteria were included: (1) older than 18 years of old; (2) ability to read and write; (3) Opioid addiction, confirmed by urine test; (4) a Pittsburgh sleep quality index score more than 5; (6) No history of neurological diseases, neuro psychosis disorder, autoimmune diseases, cancer, lung disease, heart failure class 4 or unstable angina; (7) No history of receiving benzodiazepine, anticonvulsant, aspirin, beta-blockers, calcium channel antagonists, NSAID, dexamethasone, lithium, antidepressants such as serotonin and melatonin reabsorption inhibitors; (8) Not working at night shifts; (9) Receiving MMT at least for three months; and (10) Willingness to participants. Participants were excluded if were: (1) Unwilling to continue the study; (2) Experienced changed treatment protocol; (3) History

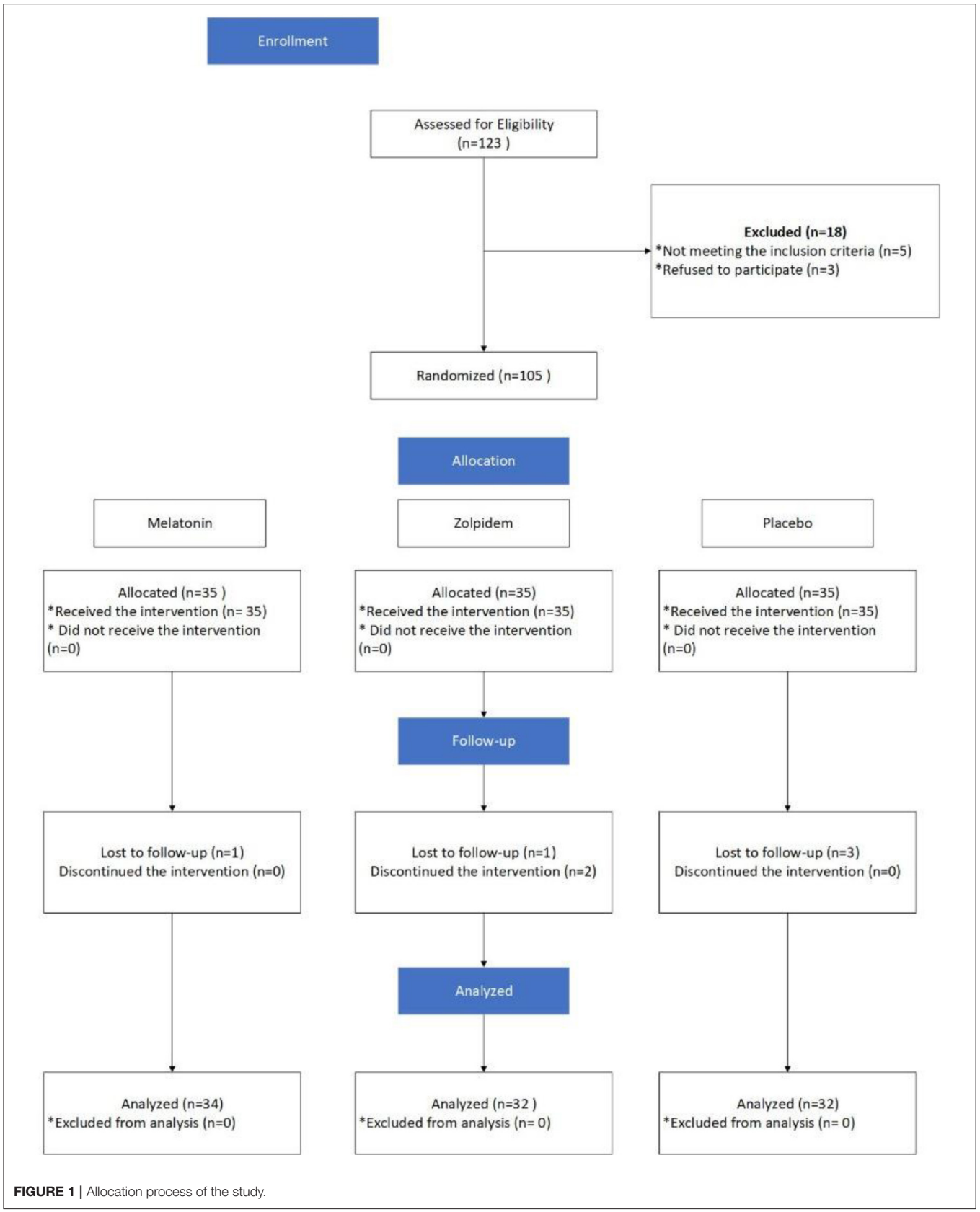

FIGURE 1 | Allocation process of the study.

of sensitivity to either melatonin or zolpidem; and (4) pregnant or breastfeeding.

Data Collection

Data were collected using a demographic questionnaire, as well as Anxiety, and Stress Scale-21 Items (DASS21), and International Index of Erectile Function (IIEF).

Depression, Anxiety and Stress Scale-21 Items

The DASS21 is a set of three self-report scales intended to measure states of depression, anxiety, and stress. Participants should score each item on a four-point Likert scale, ranging from zero ("did not apply to me at all") to three ("applied to me very much"). To obtain the total score, the scores obtained for each dimension should be summed up and then multiplied by a factor of 2. The total score ranges from zero to 120 and those for each subscale ranges from zero to 42 (25). The Persian version of the DASS21 is evaluated by NikAzin et al. and a Cronbach alpha of 0.7, 0.84, and 0.82 is reported for dimensions of depression, anxiety, and stress, respectively.

International Index of Erectile Function

Developed by Rosen and Cappelleri (26), the IIEF is a widely used scale to evaluate male sexual function. As a self-administered questionnaire, the IIEF contains 15 items that are categorized into five dimensions of erectile dysfunction, orgasm, desire, satisfaction with intercourse, and overall satisfaction. It should be noted that the first dimension is reverse scored. Hence, for other dimensions, higher scores indicate better functioning (26). Rajabi et al. (27) reported a Cronbach alpha of 0.91 for the Persian version of this scale (27).

Randomization

Initially, 123 potential subjects were proposed to participate, in which 105 of them accepted our invitation. Then, 105 participants were randomly allocated to one of the melatonin, zolpidem, and Placebo groups using random selection from a list prepared in Excel software. The latter was considered as control, and the rest were defined as intervention.

Intervention

Subjects in the zolpidem group were provided with 10 mg tablets (Manufactured by Exir Pharmaceutical Company, Boroujerd City, Iran). Participants of this group were provided with 7 tablets at the beginning of the study and were asked to refer each week for receiving new tables. In addition, they were asked take one tablet per night at bedtime. Those in the melatonin group, as MMT decreases response to routine doses of sleeping pills, were asked to take three 3 mg tablets (Razak melatonin, Karaj, Iran 3 mg = 9 mg) 30 min before sleep. Initially, a total of 21 tablets were provided to them. Those in the placebo group were given placebo tablets, made of Starch, similar to tablets in the intervention groups in shape and color (produced by a pharmacist living in the Isfahan city). The prescription dose of melatonin and zolpidem was determined based on the best efficacy of the medicines according to previous experiences of the research team. The interventions lasted for 30 days, and each participant in the zolpidem and control groups used a total of 30 tablets, while those in the melatonin group received 90 tablets. All participants were asked to refer to the center to fill the data collection tools after 30 days. In addition, they were asked to return tablets that they did not take. It is worth noting that all participants were asked to consume a regular diet and sleep in completely dark rooms to control the potential effects of nutrition status and nighttime lighting on serum levels of melatonin. Participants filled the study questionnaires two times (before and 30 days after initiating the intervention). To reduce the attrition rate, all participants were reminded of the importance of taking tablets when referring to receive in one's weekly. Furthermore, the tablets were given to participants by one member of the research team and others were unaware of the type of medicines taken by participants. The groups' allocation, interventions, and follow-up, and the analysis of the results are indicated in **Figure 1**.

Statistical Analysis

Descriptive statistics were used to summarize the collected data. The Kolmogorov-Smirnov test was applied to test for a normal distribution, which indicated a normal distribution for all variables. In addition, paired *t*-test and analysis of variance (ANOVA) were used for between-group comparisons regarding baseline variables. Partial eta squared was used to show the effect size for the ANOVAs. Bonferroni *post-hoc* test was used to compare two groups. The chi-square test was used to compare the study groups regarding the variable of occupation, marriage status, and smoking. In addition, the Kruskal-Wallis H test was used to compare the study groups regarding various levels of education. Data analysis was administered using SPSS version 23. Statistical significance was considered when $p < 0.05$. The intention to treat approach was applied.

RESULT

Initially, 105 participants were recruited, in which data of 98 of them were available for final analysis (34 in the melatonin, 32 in the zolpidem, and 32 in the placebo groups). Seven subjects were lost due to loss to follow-up, failure to receive the intervention, or reporting side effect (**Figure 1**). The youngest and oldest participants were 21 and 58 years old. The mean age of participants in the groups of melatonin, zolpidem, and placebo was 35.8±9.6 years (22 to 58 years of old), 35.9 ± 9.3 years (21 to 58), and 37.2 ± 7.8 years (26 to 53), respectively. No significant differences were observed for age and methadone dose in three groups. According to the chi-square test, there was no significant difference between the study groups concerning the variables of occupation ($p = 0.28$) and marital status ($p = 0.54$). In addition, the chi-square test with the likelihood ratio showed no significant difference between the three groups concerning the smoking status ($P = 0.93$; **Table 1**). The frequency distribution of various levels of education is also provided in **Table 1**. According to the results of the Kruskal Wallis H test, there was no significant

TABLE 1 | Comparison of demographic characteristics in the study population.

Characteristics		Melatonin	Zolpidem	Placebo	Test statistics[ł]	*P*-value
Age (year), Mean ± SD[1]		35.8 ± 9.6	35.9 ± 9.3	37.2 ± 7.8	0.233	0.79[a]
Methadone dose (mg)		17.3 ± 66.18	17.32 ± 62.88	16.32 ± 70.47	1.628	0.20[a]
Marital status	Married (%)	14 (41.2)	12 (35.5)	9 (28.1)	1.236	0.54[b]
	Single (%)	20 (58.8)	22 (64.7)	23 (71.9)		
Education level	Ability to read and write	14 (41.2)	11 (32.4)	8 (25)	0.652	0.72[c]
	Less than Diploma	14 (41.2)	17 (50)	19 (59.4)		
	Diploma	2 (5.9)	5 (14.7)	4 (12.5)		
	Bachelor	2 (5.9)	1 (2.9)	1(3.1)		
	Master's degree	2 (5.9)	0	0		
Occupation status	Employed	18 (57.9)	12 (35.3)	12 (37.5)	2.564	0.28[b]
	Unemployed	16 (47.1)	22 (64.7)	20 (62.5)		
Smoking	Yes	29 (85.3)	30 (88.2)	28 (87.5)	0.139	0.93[b]
	No	5 (14.7)	4 (11.8)	4 (12.5)		

a: ANOVA test, b: Chi-Square test; c: Kruskal Wallis H test.
1: Standard deviation.
ł Test Statistics for ANOVA: F, Test value for Chi-square test: Pearson Chi Square, Test value for Kruskal Wallis H test: Chi-square.

TABLE 2 | Comparison of changes in the scores for sexual function domains in the three groups.

Study variables		Before the intervention M ± SD	One-month after M ± SD	P[1]	P[2]	Partial eta square[$]
Erectile dysfunction	Melatonin	15.17 ± 6.82	14.76 ± 8.16	0.514	0.443	0.005
	Zolpidem	15.35 ± 7.32	14.38 ± 8.67	0.108		
	Control	14.78 ± 7.75	13.28 ± 8.85	0.014*		
Orgasmic function	Melatonin	5.82 ± 1.73	5.82 ± 1.84	0.998	0.782	0.004
	Zolpidem	5.73 ± 1.91	5.52 ± 2.10	0.456		
	Control	5.93 ± 1.74	5.71 ± 1.90	0.325		
Sexual desire	Melatonin	5.52 ± 1.65	6.64 ± 1.64	<0.0001*	0.779	0.005
	Zolpidem	5.88 ± 1.62	6.401 ± 1.79	0.034*		
	Control	6.15 ± 1.54	6.37 ± 1.68	0.415		
Intercourse satisfaction	Melatonin	6.76 ± 3.07	7.44 ± 3.98	0.191	0.273	0.026
	Zolpidem	6.91 ± 3.16	6.32 ± 3.96	0.203*		
	Control	7.09 ± 3.76	5.93 ± 3.82	0.023*		
Overall satisfaction	Melatonin	5.32 ± 2.51	6.50 ± 2.04	0.001*	0.066	0.055
	Zolpidem	5.29 ± 2.69	5.35 ± 2.46	0.863		
	Control	5.28 ± 2.72	5.34 ± 2.39	0.837		
Total	Melatonin	38.61 ± 13.38	41.17 ± 14.51	0.035*	0.672	0.008
	Zolpidem	39.17 ± 14.69	38.00 ± 16.47	0.335		
	Control	39.25 ± 15.46	38.59 ± 15.64	0.576		

P^1: Paired T-Test at 5% level; P^2: At the 5% level of multivariate ANOVA.
$: Partial Eta Square interpret: 0.01 ~ small, 0.06 ~ medium, >0.14 ~ large.
** Statically significant p value.*

difference between the study groups concerning the variable of education ($P = 0.72$). In addition, most of the participants had the ability to read and write ($n = 34$; 34%) or a degree of less than diploma ($n = 34$; 34%). There was no significant difference between the study groups concerning the variable of age, according to the one-way ANOVA test ($P = 0.79$).

Mean scores of sexual function and mental health status both before and1 month after the intervention are provided in **Tables 2**, **3**. Concerning the sexual function, those who received melatonin experienced improved sexual function (+2.56; $p = 0.035$), while subjects of zolpidem and control groups experienced reduced mean scores (−1.17 and −0.66, respectively; $p = 0.335$ vs. 0.576), which means worsened function (**Table 2**). Those in the melatonin group experienced improved scores in dimensions of sexual desire ($p < 0.0001$), and overall satisfaction ($p = 0.001$), which was not statistically significant for intercourse

satisfaction. Meanwhile, the orgasmic function and erectile dysfunction did not statically change ($p = 0.998$, 0.514). On the other hand, sexual desire ($p = 0.034$) were improved for participants in the zolpidem group. Also, the ED was declined, which indicates an improvement (−0.97; $p = 0.108$), which was not statistically significant. In addition, orgasmic function ($p = 0.456$) and intercourse satisfaction ($p = 0.203$) were reduced, while not being statistically significant. However, the reported effect size of the interventions (melatonin and zolpidem) for sexual function were small 1 month after the intervention.

For those who received the placebo, while the sexual function is declined, for dimensions of intercourse satisfaction (i.e., −1.16; $p = 0.023$), the only statistically significant improvement was related to the ED dimension ($p = 0.014$).

The results of paired *t*-test and ANOVA tests concerning the impact of the interventions on depression, anxiety and stress aspects of mental health are provided in **Table 3**. According to the findings, both interventions could significantly improve the mental health of participants ($p = 0.025$); however, only those related to the melatonin were statistically significant. Also, those in the melatonin group experienced a considerably higher improvement compared to the zolpidem group (−17.9 vs. −6.7; $p = 0.002$ and $p = 0.129$, respectively). Meanwhile, those in the placebo group experienced a slight increase in their mental health score, which indicates worsened mental health status (i.e., 0.56; $P = 0.886$), which were not statistically significant.

Concerning three dimensions of mental health (i.e., depression, anxiety, and stress), those in the melatonin group had improved scores; which was significant for depression ($p < 0.0001$) and stress ($p = 0.012$). In the same vein, subjects of the zolpidem group also had a reduced mean score, which means better health status, for all dimensions. Nevertheless, the observed improvement was not statistically significant for none of them. On the other hand, only the anxiety was slightly improved among those in the placebo group (−0.3; $p = 0.789$). Bonferroni *post-hoc* test showed that those in the melatonin group experienced more improvement compared to the other two groups in terms of depression ($p = 0.006$), while the zolpidem and control groups did not differ significantly ($p = 0.317$). In terms of anxiety, the three groups did not differ significantly. For stress dimension of the mental health; the mean score in the zolpidem group was not significantly different from the other two groups ($p = 0.587$, $p = 0.353$), but the melatonin group was significantly better than the control group ($p = 0.015$). so that an improvement equal to (−17.09) was observed in the melatonin group compared to (−6.7) in the zolpidem group ($p = 0.002$ vs. $p = 0.129$). Melatonin had the greatest effect on the dimension of depression, which had the highest effect size) partial eta squared = 0.197).

DISCUSSION

There are evidence indicating the negative impacts of both opioid addiction and MMT on mental health (28) and sexual function (17). In the present study, we investigated the impact of melatonin and zolpidem on these outcomes, and a comparison is provided concerning their effects, using a placebo group.

Sexual dysfunction is defined as psychophysiological changes that affect the sexual response cycle and cause impaired sexual desire (29). The association between depression and declined sexual function is well-established, particularly through decreased libido and ED (30). There are evidence indicating that melatonin can improve sexual function by declining the arousal threshold by moderating the sensitivity of the central 5-hydroxytryptaminergic receptor (31). However, it should be considered that various factors contribute to sexual function, including sex, education, depression, and socio-economic status (32), in which some of them are controlled in the present study. Other possible reasons for the positive impacts of melatonin on sexual function are reduced oxidative stress and preventing cell apoptosis in the central nervous system.

TABLE 3 | Comparison of changes in the scores for mental health domains in the three groups.

Study variables		Before the intervention M ± SD	One-month after M ± SD	P^1	P^2	Partial eta squared[$]
Depression	Melatonin	20.9 ± 9.7	12.5 ± 6.9	<0.0001	0.0001	0.197
	Zolpidem	20.2 ± 6.7	17.9 ± 7	0.120		
	Control	20.1 ± 7.5	20.7 ± 7.03	0.668		
Anxiety	Melatonin	18.9 ± 8.5	15.6 ± 8.3	0.103	0.06	0.056
	Zolpidem	18 ± 5.8	15.4 ± 6.6	0.089		
	Control	19.4 ± 6.4	19.1 ± 5.4	0.789		
Stress	Melatonin	20.8± 8.9	15.5 ± 8.2	0.012	0.019	0.078
	Zolpidem	19.7 ± 5.7	17.9 ± 7.9	0.340		
	Control	20.5 ± 7.3	20.8 ± 6.2	0.842		
Total	Melatonin	60.65 ± 24.12	43.56 ± 19.42	0.002	0.025	0.128
	Zolpidem	57.88 ± 16.08	51.18 ± 19.30	0.129		
	Control	60.00 ± 18.97	60.56 ± 15.78	0.886		

P^1: Paired T-Test at 5% level; P^2: At the 5% level of multivariate ANOVA.
$: Partial Eta Square interpret: 0.01 ~ small, 0.06 ~ medium, >0.14 ~ large.

The results of the present study showed that melatonin could significantly improve the mean score of sexual function and mental health. The highest improvement was for the dimension of overall satisfaction (1.18), followed by sexual desire (1.12), intercourse satisfaction (0.68), and ED (−0.041). While no change was observed for orgasm function. In the same vein, following a randomized placebo-controlled trial, Parandavar et al. (31) reported improved sexual function mean score for those who received melatonin (31). Furthermore, some animal studies also suggested improvements in the sexual function of rats following melatonin administration (33, 34). As mentioned before, opioid addiction causes several mental health issues. In this line, there are evidence regarding the positive effect of melatonin on oxidative stress, which in turn translates into better mental health (35, 36). Our findings indicated the considerable impact of melatonin on investigated dimensions of mental health. Similarly, Shabani et al. (37), who studied the impact of melatonin administration on mental health parameters in women with polycystic ovary syndrome following a randomized, double-blind, placebo-controlled trial, reported positive effects of melatonin on mental health (37). In a clinical randomized trial on those under MMT, Ghaderi et al. (21) reported similar results concerning the impact of melatonin on mental health (21).

zolpidem is an imidazopyridine, a non-benzodiazepine with sedative-hypnotic effects that is widely used to treat mental health issues, mainly due to its high absorption rate. Hence, it can be consumed later in the night without worrying about residual cognitive impairment the next morning (38). In addition, zolpidem is known for its rapid action and low residual and rebound effects. In the present study, zolpidem only was associated with significant improvement in the sexual desire dimension. In addition, its effect was lower than that of melatonin for both investigated outcomes. zolpidem did not cause improved mental health status. While this finding is in line with some studies such as that of Eslami-Sharbabaki et al. (39), it is not in line with several other studies. For instance, Dang et al. (38) reported significant effects on the management of mental health issues in subjects with drug abuse (38). Or in a randomized controlled study, Shakya et al. (40) reported positive effects of 10 mg zolpidem on sleep quality, pain management, and reducing depression (40). This difference can be attributed to factors such as low dose of the drug or short follow-up period of our study. In this study, we examined the effect of 1 month of zolpidem, although various studies have reported side effects such as the risk of suicide, rebound insomnia, falls, hip fractures, etc. in long-term use or with high doses of this drug, and this point should be considered in the administration of zolpidem (41, 42).

According to the best knowledge of the authors, no study has compared the effect of melatonin and zolpidem concerning either sexual function or mental health; hence, we couldn't find comparable findings to mention in this study. Eventually, it should be noted that some evidence indicated a gender difference concerning the effect of zolpidem on sexual function, with higher levels of plasma concentrations in women (43).

In Iran, besides methadone treatment protocol, there is no standard treatment for patients' psychological and sexual problems. Therefore, the results of this study can help addiction therapists to manage their patients' problems.

Limitations

It is necessary to mention some limitations of our study, including the withdrawal of some participants, short follow up period, intervention only on male gender and being a single center study. Hence, caution should be taken when generalizing the findings.

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 the Research Ethics Committee of the Isfahan University of Medical Sciences approved and supported the trial (code IR.MUI.MED.REC.1399.813). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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

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The Association of P300 Components With Clinical Characteristics and Efficacy of Pharmacotherapy in Alcohol Use Disorder

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Purpose: The purpose of this study is to explore the association of P300 components with clinical characteristics and efficacy of pharmacotherapy in alcohol use disorder (AUD).

Methods: One hundred fifty-one AUD patients and 96 healthy controls were recruited and evaluated for the symptoms of depression, anxiety, sleep, and cognitive function by the Alcohol Use Disorders Identification Test (AUDIT), the 9-item Patient Health Questionnaire (PHQ-9), the 7-item Generalized Anxiety Disorder scale (GAD-7), the Pittsburgh Sleep Quality Index (PSQI), Digit Symbol Substitution test (DSST), and event-related potential P300, which is one of the averaged scalp electroencephalography responses time-locked to specific events. Among the AUD group, 101 patients finished an 8-week pharmacotherapy and were evaluated for the above data at post-intervention.

Results: 1. At baseline, AUD patients had higher scores of AUDIT, PHQ-9, GAD-7, PSQI, and P300 latency at Cz, Pz, and Fz and lower DSST score and smaller P300 amplitudes at Fz, Cz, and Pz compared with controls. P300 components correlated significantly with alcohol dose and score of AUDIT, PHQ-9, GAD-7, PSQI, and DSST. 2. After 8 weeks' treatment, there were significant changes for the P300 components; alcohol dose; and score of AUDIT, PHQ-9, GAD-7, PSQI, and DSST. Variables at baseline, including P300 amplitudes at Fz, Cz, and Pz; latency of Fz and Pz; alcohol dose; and scores of PHQ-9, GAD-7, PSQI, and DSST, were significantly associated with changes of reduction rate of AUDIT scores. However, P300 amplitudes at Fz, Cz, and Pz in AUD patients after 8-week treatment were still significantly shorter than healthy controls (HCs), and P300 latencies at Fz, Cz, and Pz were significantly longer than HCs. 3. When validated area under the receiver operating characteristic curve (AUC) was over 0.80, the baseline variables including amplitudes at Cz and Pz, alcohol dose, and scores of PSQI could predict the changes of reduction rate of AUDIT score.

Conclusion: P300 amplitudes and latencies at Fz, Cz, and Pz could be used as biological markers for evaluating the clinical characters and severity of AUD. P300 amplitudes at Cz and Pz, sleep condition, and cognitive function at baseline could predict the efficacy of pharmacotherapy for AUD patients.

Keywords: alcohol use disorder (AUD), P300 components, efficacy, biological markers, pharmacotherapy

INTRODUCTION

About 31 million people suffer from substance use disorders (SUD) worldwide (1). Among them, alcohol use disorder (AUD) is a major problem. AUD or alcoholism is defined as a problematic pattern of alcohol use accompanied by clinically significant impairment or distress (2) and now is also a severe health issue and a high economic burden on society. From the China Mental Health Survey, the weighted lifetime prevalence of AUD was 4.4%, becoming the most prevalent substance use disorder in China (3).

AUD is frequently accompanied by co-occurring psychiatric disorders or somatic disorders, such as drug use disorders, major depressive disorder, bipolar disorder I, and anxiety disorders (4). In a cross-sectional survey of 2,979 individuals with AUD, 77% reported a moderate-to-severe psychiatric or somatic disorder. Those with both AUD and a psychiatric or somatic disorder had poorer associated health-related quality of life and lower work productivity than those with AUD only (5). Due to the effects of alcohol on brain structures and subsequent alterations in neuronal function, alcohol has sedative and detrimental effects on both performance and cognitive functioning (6), resulting eventually in neurodegeneration and cognitive impairment (7).

Electrophysiological variables may represent sensitive biomarkers of vulnerability to, or endophenotypes for, AUD (8). Event-related potentials (ERPs) are averaged scalp electroencephalography responses time-locked to specific events in a sensory, motor, or cognitive task. The averaged responses or waveforms of ERP are composed of characteristic negative and positive deflections. Amplitude (μV) is defined as the difference between the mean prestimulus baseline voltage and the largest positive-going peak of the ERP waveform within a time window. Latency (ms) is defined as the time from stimulus onset to the point of maximum positive amplitude within a time window (9). One component of ERP, P300 is a large, long-lasting component observed between 300 and 700 ms at central-parietal sites after onset of visual or auditory stimuli (10). In the detection of P300, oddball paradigms are widely used to evaluate cognition. The traditional two-stimulus oddball presents an infrequent target in a background of frequent standard stimuli (9). The P300 waveform includes P3a and P3b. P3a is elicited by novel or non-target stimuli of the traditional oddball task, whereas P3b is elicited by target stimuli of the traditional oddball task (11). The P300 has been associated with a wide range of attention, memory, and premotor decisional processes, along with response inhibition, which is a common characteristic and impaired in AUD (12, 13). In some studies, reduced amplitudes and increased latencies of the P300 component compared to control subjects have been found in AUD patients (14, 15). Variables of the P300 component have also been associated with an impaired behavior control and a higher relapse probability (9, 16). As subcomponents of P300, amplitudes of P3a and P3b were found reduced in AUD patients (11, 17). Now this evidence indicates that the P300 component is considered a potential endophenotype for vulnerability to develop AUD, a predictor and biomarker for the relapse risk after alcohol withdrawal (18).

A previous study found that the relationship of prolonged P300 latency and reduced P3 amplitude with impairment of auditory information processing in schizophrenia was not influenced by neuroleptic medication (19). In another study of antidepressant response, greater baseline P3a/b amplitudes were associated with a positive antidepressant response (20). In a recent study, compared to healthy controls, AUD patients presented reductions of P3a/3b amplitude, and, after 4-week alcohol abstinence, although P3a/3b amplitudes were improved, they were still lower than those of healthy controls (11). Given the important role of P300 amplitudes and latencies in AUD, could these components reflect the efficacy of treatment in AUD? Up to now, there has been little research into the P300 component in the treatment of AUD; therefore, in this study, we aimed to explore the association of P300 amplitudes and latencies with the efficacy of treatment in AUD. We hypothesized that AUD severity, negative emotion (depression and anxiety), cognitive function, and worse treatment response would be associated with a blunted and delayed P3. We also hypothesized that P300 amplitudes and latencies would change with treatment but would still be worse than those of healthy controls.

MATERIALS AND METHODS

Subjects

A cohort of 151 subjects of male AUD was recruited from the Second Affiliated Hospital to Kunming Medical University, Mental Health Hospital of Qujing, and Mental Health Hospital of Yunnan Province. All patients met the criteria for Diagnosis and Statistics of Mental Disorder 5th edition (DSM-V) for AUD with normal vision and hearing or within the normal range after correction and were right handed. The exclusion criteria were (1) diagnosis of other substance use disorders; (2) history of head injury, neurological disorders, or loss of consciousness; (3) history of diabetes, stroke, or hypertension that required medical intervention; (4) clinical evidence of Wernicke–Korsakoff syndrome; (5) having evidence of mental retardation and any pervasive developmental disorder; (6) having comorbid diagnoses of schizophrenia, obsessive compulsive disorder, and post-traumatic stress disorder because comorbid

TABLE 1 | Comparison of clinical and ERP data between control group and alcoholic group.

Variable	Control group ($n = 96$)	Alcoholic group (n =1 51)		*P* value
Age	45.2 ± 7.1	51.9 ± 8.0	$T = -6.676$	<0.001
Education years	14 [4]	15 [4]	$Z = -1.710$	0.087
Marriage			$X^2 = 11.179$	0.001
Married	89 (92.7)	115 (76.2)		
Divorced	7 (7.3)	36 (23.8)		
Dose (ml/day)	–	150 [100]		
Drink duration (y)	–	15 [12]		
PHQ-9	3.26 ± 0.65	15.63 ± 1.87	$T = -62.42$	<0.001
GAD-7	2.89 ± 0.64	15.24 ± 1.89	$T = -61.77$	<0.001
PSQI	3.46 ± 0.59	13.63 ± 1.79	$T = -53.81$	<0.001
DSST	33.64 ± 2.15	18.27 ± 2.89	$T = 42.83$	<0.001
Amplitude (μV)				
Fz	14.62 [1.17]	9.12 [0.47]	$Z = 13.009$	<0.001
Cz	13.17 [1.71]	8.76 [0.95]	$Z = 13.168$	<0.001
Pz	11.38 [1.26]	8.67 [0.95]	$Z = 12.466$	<0.001
Latency (ms)				
Fz	320 [46]	432 [34]	$Z = -12.734$	<0.001
Cz	334 ± 48	435 ± 29	$T = -18.503$	<0.001
Pz	336 [61]	446 [51]	$Z = -12.422$	<0.001

Data are presented as mean ± SD, median [interquartile range] or absolute numbers (percentage).

AUD and PTSD or OCD could lead to a high rate of treatment dropout (21, 22); (7) having serious suicidal ideation or serious attempted suicide. AUD patients were also interviewed on their lifetime use of alcohol and abused substances. These procedures yielded alcohol average dose, alcohol peak dose, and duration; and (8) having no more than 50 trials in the target or non-target averages.

A group of 96 male healthy controls (HC) were recruited from the Health Management Center of the Second Affiliated Hospital to Kunming Medical University or local community. For HC, the exclusion criteria included (1) current substance abuse or dependence; (2) history of substance dependence; (3) a current or previous mental illness (or/and treatment); (4) history of head injury, neurological disorders, or loss of consciousness; (5) without normal vision or hearing or out of range after correction; (6) history of diabetes, stroke, or hypertension that required medical intervention; and (7) left handed.

The study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital to Kunming Medical University. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. The registration number of this study is NTC 03910686.

Measures

The Alcohol Use Disorders Identification Test

The Alcohol Use Disorders Identification Test (AUDIT) (23, 24) is a 10-item alcohol-screening questionnaire that was specifically designed to avoid cultural bias. The instrument had been validated (25) and used in Chinese alcohol research (26). The cutoff of AUDIT in China was determined as 7, and the higher the score, the more severe the symptoms of AUD (25).

TABLE 2 | The association between ERP data and clinical data by Spearman simple correlation in all included AUD patients by Bonferroni correction ($N = 151$).

	Am-Fz	Am-Cz	Am-Pz	La-Fz	La-Cz	La-Pz
Dose	−0.470*	−0.694*	−0.699*	0.576*	0.438*	0.494*
Drink duration	−0.498*	−0.819*	−0.857*	0.574*	0.504*	0.519*
PHQ-9	−0.614*	−0.450*	−0.463*	0.395*	0.494*	0.395*
GAD-7	−0.548*	−0.448*	−0.501*	0.473*	0.445*	0.421*
PSQI	−0.392*	−0.447*	−0.500*	0.355*	0.311*	0.344*
DSST	0.622*	0.579*	−0.609*	−0.530*	−0.563*	−0.498*

Bonferroni correction:$\alpha = 0.05/6 = 0.008$, $^*p < 0.008$.

The 9-Item Patient Health Questionnaire, the 7-Item Generalized Anxiety Disorder Scale, and the Pittsburgh Sleep Quality Index

Chinese versions of the 9-item Patient Health Questionnaire (PHQ-9), 7-item Generalized Anxiety Disorder scale (GAD-7), and Pittsburgh Sleep Quality Index (PSQI) with established reliability and validity were used to assess the severity of depression, anxiety, and insomnia. Subjects completed three self-administered scales: PHQ-9 (27), GAD-7 (28), and PSQI (29).

Symptom severity was defined as mild, moderate, or severe using the following cutoffs: scores of 6, 12, and 15 on the PHQ-9 for depression (30) and 4, 9, and 12 on the GAD-7 for generalized anxiety (31). Since there are no established severity cutoffs for

TABLE 3 | The association between ERP data and clinical data by Spearman simple correlation in follow-up AUD patients by Bonferroni correction ($N = 101$).

	Am-Fz	Am-Cz	Am-Pz	La-Fz	La-Cz	La-Pz
Dose	−0.653*	−0.748*	−0.740*	0.683*	0.595*	0.599*
Drink duration	−0.623*	−0.759*	−0.778*	0.658*	0.626*	0.566*
PHQ-9	−0.603*	−0.492*	−0.511*	0.490*	0.621*	0.466*
GAD-7	−0.589*	−0.498*	−0.534*	0.533*	0.520*	0.404*
PSQI	−0.582*	−0.571*	−0.603*	0.605*	0.548*	0.453*
DSST	0.748*	0.753*	0.793*	−0.689*	−0.703*	−0.624*
Reduction rate of AUDIT	0.593*	0.652*	0.688*	−0.584*	−0.484*	−0.549*

*Bonferroni correction: $\alpha = 0.05/7 = 0.007$, *$p < 0.007$.*

the Chinese version of the PSQI, the continuous score of the instrument was used to establish severity, with higher scores indicating worse sleep quality.

Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST) is a valid measure of cognitive dysfunction impacted by many domains, including motor speed, attention, processing speed, executive functioning, and working memory, and is sensitive to the presence of cognitive dysfunction as well as to change in cognitive function across a wide range of clinical populations (32, 33). DSST had been used in clinical neuropsychology in China (34, 35). Because there is no gold standard regarding the threshold score for which the DSST indicates cognitive impairment, the lowest quartile in the study (≤28 points) was defined poor cognitive performance, or DSST impairment, consistent with methods previously published (36).

ERP P300 Recording

P300 was detected by the same methods as our previous reports (37).

Paradigm

An auditory oddball paradigm with 80% non-target stimuli (540 tones, 1,000 Hz) and 20% target stimuli (135 tones, 2,000 Hz) presented binaurally through headphones in a pseudo randomized order was used (80 dB SPL, 40-ms duration with 10-ms rise-and-fall time, and inter stimulus interval 1.5 s). Subjects were seated with their eyes closed in a reclining chair and had to press a button with their dominant hand after target stimuli. P300 recordings were measured automatically, and the researcher of P300 was blind to disease status and genotype status.

Recording

Recording took place in a sound-attenuated and electrically shielded room adjacent to the recording apparatus (Niclolet MEGA). Subjects were seated with closed eyes in a slightly reclined chair with a head rest. Evoked potentials were recorded with electrodes Fz, Cz, and Pz. The reference electrodes were A1 and A2. A1 and A2 were linked. The electrodes were positioned according to the International 10/20 system. Fpz served as ground. Electrode impedance was <10 kΩ. Data were collected with a sampling rate of 250 Hz and an analogous band pass filter (0.16–50 Hz). After channels were selected (Fz, Cz, and Pz), data were averaged per condition (target vs. non-target) in which only segments with correct behavioral responses were included in the average and represented graphically in terms of latency (x-axis) and amplitude (y-axis). The P300 component was identified as the most positive component within the latency window of 250–600 ms. For artifact suppression, an amplitude criterion has been used (77 mV) involving three channels at any time point during the averaging period. Only wave shapes based on at least 50 averages were accepted. The P300 amplitude and latency at all electrodes for the target stimulus were determined automatically after detection by the computerized program.

TABLE 4 | Comparison of completers and dropouts of AUD group.

Variable	Completers ($n = 101$)	Drop-outs ($n = 50$)	Statistical value	*P*
Age	51.9 ± 7.9	51.7 ± 8.3	$T = 0.144$	0.886
Education years	15 [4]	15 [4]	$Z = -0.141$	0.888
Marriage			$X^2 = 0.140$	0.709
Married	76 (75.2)	39 (78)		
Divorced	25 (24.8)	11 (22)		
Dose (ml/day)	150 [100]	160 [100]	$Z = -0.558$	0.577
Drink duration (y)	15 [12]	15 [13]	$Z = -0.389$	0.697
PHQ-9	15.8 ± 1.7	15.9 [3.0]	$Z = -0.740$	0.459
GAD-7	16.0 [3.0]	15.3 [2.0]	$Z = -0.989$	0.323
PSQI	13.7 ± 1.8	14.0 [2.0]	$Z = -0.802$	0.423
DSST	18.5 ± 3.2	17.9 ± 2.3	$T = 1.079$	0.282
Amplitude (μV)				
Fz	9.01 ± 0.47	9.21 ± 0.39	$T = -1.609$	0.110
Cz	8.74 [0.96]	8.88 ± 0.61	$Z = -0.836$	0.403
Pz	8.65 [0.89]	8.90 ± 0.73	$Z = -0.789$	0.430
Latency (ms)				
Fz	425.3 ± 22.7	436.9 ± 29.4	$T = -2.666$	0.009*
Cz	425 (38)	443.5 ± 33.8	$Z = -2.163$	0.031*
Pz	443.9 ± 31.1	445.0 ± 34.2	$T = -0.201$	0.841

$p < 0.05$.

Procedure

All 151 AUD patients and 96 controls were evaluated by using AUDIT, PHQ-9, GAD-7, PSQI, DSST, and P300 detection after they were recruited at the baseline. For the AUD patients, as

TABLE 5 | Change of outcome measures after 8 weeks pharmacotherapy intervention ($n = 101$) and comparison between the post-intervention AUD group ($n = 101$) and healthy controls (HC) ($n = 96$).

Variable	Pre- ($n = 101$)	Post- ($n = 101$)	HC ($n = 96$)	Pre- vs. post-		Post- vs. HC	
				Statistical value	*P*	Statistical value	*P*
Am-Fz (μV)	9.12 [0.61]	9.89 ± 1.01	14.62 [1.17]	$Z = -8.595$	<0.001*	$Z = 11.888$	<0.001
Am-Cz (μV)	8.78 ± 0.76	9.89 [2.12]	13.17 [1.71]	$Z = -8.725$	<0.001*	$Z = 10.788$	<0.001
Am-Pz (μV)	8.74 ± 0.85	9.89 [2.19]	11.38 [1.26]	$Z = -8.618$	<0.001*	$Z = 7.687$	<0.001
La-Fz (ms)	428.1 ± 28.5	401.1 ± 33.4	320 [46]	$T = 20.212$	<0.001*	$Z = -10.085$	<0.001
La-Cz (ms)	425.0 [35.0]	399.0 [44.0]	334 ± 48	$Z = 8.602$	<0.001*	$Z = -8.936$	<0.001
La-Pz (ms)	440.0 ± 32.1	412.1 ± 39.5	336 [61]	$T = 16.129$	<0.001*	$Z = -9.472$	<0.001
Dose 1 (ml/day)	172.9 ± 59.2	90.0 [110.0]	–	$Z = 8.563$	<0.001*	–	–
Dose 2 (g/day)	99.0 [47.0]	49.5 [69.0]	–	$Z = 8.590$	<0.001*	–	–
AUDIT	34.0 [9.0]	27.0 [14.0]	–	$Z = 8.631$	<0.001*	–	–
PHQ-9	16.42 ± 2.29	9.86 ± 2.01	3.26 ± 0.65	$T = 40.777$	<0.001*	$T = 30.680$	<0.001
GAD-7	15.62 ± 1.66	9.67 ± 2.33	2.89 ± 0.64	$T = 43.299$	<0.001*	$T = 27.537$	<0.001
PSQI	14.12 ± 1.88	8.88 ± 2.50	3.46 ± 0.59	$T = 33.956$	<0.001*	$T = 20.699$	<0.001
DSST	18.41 ± 3.75	22.02 ± 4.63	33.64 ± 2.15	$T = -22.105$	<0.001*	$T = -22.399$	<0.001

*Data are presented as mean ± SD or median [interquartile range]. Pre-post comparison was analyzed by paired tests, while post-HC comparison was analyzed by independent tests, and corrected by Bonferroni test: $\alpha = 0.05/2 = 0.025$, *$p < 0.025$.*

they finished these assessments, they were invited to attend an 8-week in-patient pharmacotherapy intervention after they gave informed consent for the research. Then, at the end of 8 weeks, they were evaluated again for the above psychological assessments and P300. In this study, all the AUD patients did not receive any kind of concurrent psychosocial treatment.

The primary outcomes were the changes of average alcohol dose/day and AUDIT scores from baseline to end point after an 8-week pharmacotherapy intervention. The second outcomes were the changes of PHQ-9, GAD-7, PSQI, DSST, and P300 from baseline to the 8-week end point after pharmacotherapy intervention.

Pharmacotherapy Intervention Protocol

According to the treatment recommendations in the recently issued "Guidelines for the Diagnosis and Treatment of Mental Disorders in China (2020)" (38), benzodiazepine substitution therapy is recommended for AUD patients, especially for the patients of alcohol dependence. In the guidelines, the recommended dose of benzodiazepine is 10 mg at the beginning, and the highest end of the recommended range is 30–40 mg/day. The duration of treatment is from 5 days to 2 weeks, and then, the dose is gradually decreased and finally stopped in order to avoid the dependence on benzodiazepine. In addition, antipsychotics or antidepressants could be prescribed if the patients have co-occurring psychiatric disorders or psychiatric symptoms. When psychiatric symptoms persist despite a substantial reduction or cessation in drinking, the optimal approach is to continue the alcohol pharmacotherapy and add a specific psychiatric medication (39). Therefore, in this pharmacotherapy intervention, patients could be also given antidepressants if they had persistent symptoms, such as depression or anxiety symptoms.

According to the Guidelines for the Diagnosis and Treatment of Mental Disorders in China (2020), all AUD patients were prescribed benzodiazepine when they finished the initial assessment. Titration was allowed for the first week, and all subjects were treated from doses in the lower end of the recommended range, 10 mg/day, to the highest end of the recommended range, 30 mg/day. The benzodiazepine dose was allowed to decrease in response to emergence of side effects, such as excessive sedation and difficulty breathing. The titrated dose was then kept constant for 2 weeks. From the fourth week to the end of the fifth week, in order to avoid dependence on benzodiazepine, the dose was decreased from the titrated dose to withdrawal.

Antidepressant drugs were prescribed for AUD patients with comorbid major depressive disorder (MDD) or GAD according to local best practice. Titration was allowed for the first 2 weeks, and all subjects were initially treated with doses in the lower end of the recommended ranges (fluoxetine: 10 mg/day, paroxetine: 10 mg/day, sertraline: 25 mg/day, venlafaxine-XR: 37.5 mg/day, and duloxetine hydrochloride: 15 mg/day). The dose was increased after the first week. In exceptional cases (i.e., for subjects showing no serious response such as nausea, vomiting, diarrhea, indigestion, and other side effects observed at usual clinical prescribing dose), the dose could then be increased further at the second weekend, then up to a maximum daily dose at the higher end of recommended ranges (fluoxetine: 60 mg/day, paroxetine: 60 mg/day, sertraline: 200 mg/day, venlafaxine-XR: 225 mg/day, and duloxetine hydrochloride: 120 mg/day). The dose was then kept constant for 8 weeks.

Statistical Analysis

Statistical analyses were performed by SPSS 25.0 (Statistical Package for Social Sciences, IBM, Armonk, NY) and MedCalc Statistics v19.6.3 (MedCalc Software bvba, Ostend, Belgium).

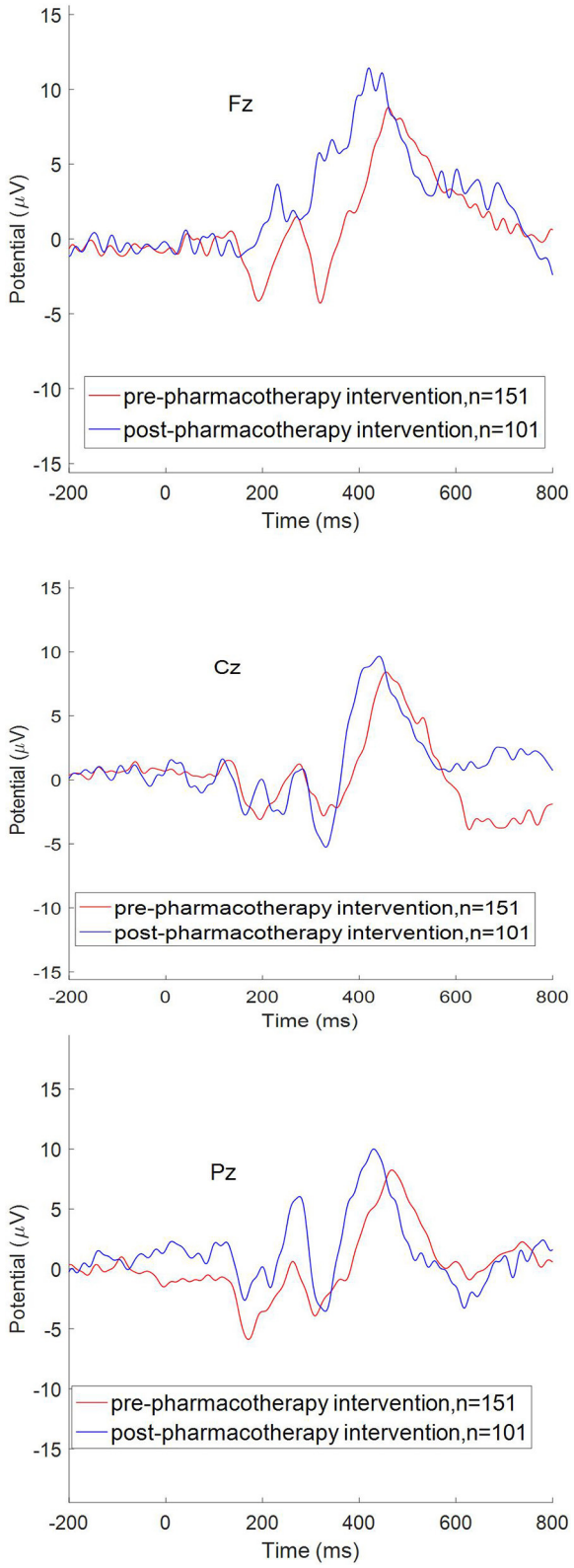

FIGURE 1 | P300 (Fz Cz Pz) pre-pharmacotherapy intervention and post.

Continuous data were presented as mean ± standard deviation (SD) or median (interquartile range). Categorical data were presented as absolute numbers and percentages. The expectation maximization (EM) method was used in missing data imputation. There were 19 random missing data of PHQ-9, GAD-7, PSQI, and DSST from drop-outs (38%), which were filled by the EM method.

A multi-level model was used to compare the outcome variables between pre-treatment and post-treatment as the outcome variable at level 1 and the participant at level 2.

Associations between changes in ERP data and symptoms were analyzed by Spearman correlation analysis. Univariate and multivariate linear regressions were analyzed using the reduction rate of AUDIT as the dependent variable, while the pre-intervention ERP data and psychometric scales as the independent variables.

Based on the frequencies and distributions of the reduction rate of AUDIT scores [reduction rate = (pre-treatment score – post-treatment score) / pre-treatment score × 100%], a better therapeutic effect on alcohol dependence in this research was defined as the reduction rate of AUDIT score of ≥20%, which was around the second quartile, and accordingly, the patients were classified into the effective group (n = 53, 52.5%) and the ineffective group (n = 48, 47.5%). Binary logistic regression analysis was used to explore if changes in ERP data and psychometric scales could predict a better therapeutic effect on alcohol dependence. We used a receiver operating characteristic (ROC) curve to compare the overall accuracy of the variables associated with better therapeutic effect. The area under the ROC curve (AUC) and 95% confidence interval (CI) were calculated. The larger the AUC is, the better the overall diagnostic accuracy is. The comparisons between ROC curves were performed by the DeLong method. We used a two-sided α of 0.05 for statistical significance.

RESULTS

Demographic and Clinical Characteristics of AUD and HC Groups at Baseline

There were 151 AUD patients and 96 HC recruited at the baseline. As shown in **Table 1**, the average age of AUD was 52 ± 8 years, which was significantly older than HC. So, in the analysis of DSST and P300, age was used as a covariant to exclude the effect of age on cognitive differences. The AUD group had a higher rate of divorce than HCs. There were 14 subjects in the AUD group who had a positive family history for mental illnesses. In the AUD group, there were 79 subjects in working status, 40 subjects who were retired, and 32 subjects in unemployed status. Among the total 151 subjects in the AUD group, 32 subjects had received treatment for alcoholism.

In the AUD patients, according to the symptom severity of PHQ-9 at baseline, there were 85 cases comorbid with depression symptoms to a severe degree (56.3%), 36 cases with moderate depression (23.8 %), 14 cases with mild depression (9%), and

TABLE 6 | The result of multi-level model analysis.

Variable	Pre- ($n = 151$)	Post- ($n = 101$)	*F*	*P*
Am-Fz (μV)	9.12 [0.47]	9.89 ± 1.01	51.477	<0.001*
Am-Cz (μV)	8.76 [0.95]	9.89 [2.12]	52.398	<0.001*
Am-Pz (μV)	8.67 [0.95]	9.89 [2.19]	46.328	<0.001*
La-Fz (ms)	432 (38)	401.1 ± 33.4	51.320	<0.001*
La-Cz (ms)	435 ± 29	399.0 [44.0]	67.189	<0.001*
La-Pz (ms)	446 (40)	412.1 ± 39.5	46.623	<0.001*
Dose (ml/day)	172.9 ± 59.2	90.0 [110.0]	41.779	<0.001*
PHQ-9	15.63 ± 1.87	9.86 ± 2.01	474.520	<0.001*
GAD-7	15.24 ± 1.89	9.67 ± 2.33	364.714	<0.001*
PSQI	13.63 ± 1.79	8.88 ± 2.50	247.889	<0.001*
DSST	18.27 ± 2.89	22.02 ± 4.63	45.871	<0.001*

*Data are presented as mean ± SD or median [interquartile range]. *$p < 0.05$.*

16 cases without symptoms of depression (10.9%). According to symptom severity from GAD-7, there were 82 cases comorbid with anxiety symptoms to a severe degree (54.3%), 28 cases with moderate anxiety (18.5%), 15 cases with mild anxiety (9.9%), and 26 cases without symptoms of anxiety (17.3%). The score of PSQI in AUD was significantly higher than that of HCs. The score of DSST in the AUD group was significantly lower than that of the HC group.

Also shown in **Table 1**, P300 amplitudes at Fz, Cz, and Pz in the AUD group were significantly smaller than those in the HC group. P300 latency at Fz, Cz, and Pz in the AUD group was also significantly longer than that of the HC group. Both in the AUD and HC groups, the amplitude was the largest and latency was the shortest for Fz among the three electrodes.

The Relationship of P300 Data With Other Clinical Data in AUD Patients

As shown in **Tables 2**, **3**, Spearman correlation analysis after Bonferroni correction showed that both for all AUD patients at baseline and for the patients after pharmacotherapy intervention, P300 amplitudes at Fz, Cz, and Pz correlated negatively with average alcohol dose; drinking duration; and scores of PHQ-9, GAD-7, and PSQI, but correlated positively with the score of DSST. P300 latency at Fz, Cz, and Pz correlated positively with average alcohol dose; drinking duration; and scores of PHQ-9, GAD-7, and PSQI, but correlated negatively with the score of DSST.

Therapeutic Effects of Pharmacotherapy Intervention on Average Alcohol Dose and Scores of AUDIT, PHQ-9, GAD-7, PSQI, and P300 in the AUD Patients

In total, there were 101 patients who finished the 8-week pharmacotherapy intervention. In the pharmacotherapy intervention, the average dose of benzodiazepine each day was 20.72 ± 8.64 mg/day, and the average daily dose for each antidepressant was consistent with usual clinical prescribing practices (fluoxetine: 30 ± 9 mg/day, paroxetine: 30 ± 10 mg/day, sertraline: 75 ± 25 mg/day, venlafaxine-XR: 115 ± 30 mg/day, and duloxetine hydrochloride: 60 ± 30 mg/day).

Except for the latencies of Fz and Cz, there were no significant differences for age; education; marriage status; drinking dose; and symptom duration of PHQ-9, GAD-7, and PSQI; scores of DSST; amplitudes of Fz, Cz, and Pz; and latency of Pz between completers and dropouts of the AUD group, as shown in **Table 4**.

As shown in **Table 5** and **Figure 1**, after an 8-week treatment, average alcohol dose; P300 latencies at Fz, Cz, and Pz; and scores of AUDIT, PHQ-9, GAD-7, and PSQI all decreased significantly. P300 amplitudes at Fz, Cz, and Pz and the score of DSST increased significantly. However, even after the 8-week treatment, P300 amplitudes at Fz, Cz, and Pz in AUD patients were significantly shorter than HCs, and P300 latencies at Fz, Cz, and Pz in AUD patients were significantly longer than HCs. Scores of PHQ-9, GAD-7, and PSQI were still higher than HCs, and scores of DSST after the 8-week treatment were still lower than HCs, as shown in **Table 5**. **Table 6**, by a multi-level model, also demonstrates the same results between the completer subsample ($n = 101$) as well as the entire sample ($n = 151$).

As shown in **Tables 7**, **8**, the linear regression analysis and binary logistic regression analysis exploring the therapeutic effect of pharmacotherapy confirmed the above results. P300 amplitudes at Fz, Cz, and Pz; the latency of Fz, Cz, and Pz; and scores of PHQ-9, GAD-7, PSQI, and DSST at baseline were all significantly associated with the changes of reduction rate of AUDIT scores.

When validated AUC was over 0.80, the variants of baseline, namely, amplitudes at Cz and Pz and scores of PSQI and DSST, could predict the reduction rate of AUDIT scores after pharmacotherapy intervention, as shown in **Table 9** and **Figures 2**, **3**.

DISCUSSION

In the present study, all AUD patients had depressive or anxiety symptoms and sleep disturbances, such as insomnia. Among them, 89.1% patients were comorbid with depression, and 80.1% of them could be rated as having a moderate or severe degree of depressive symptoms. Furthermore, 82.7% patients were comorbid with anxiety, and 72.8% of them could be rated as having a moderate or severe degree of anxiety symptoms. There is considerable comorbidity between AUD and MDD or GAD (41). Results from the 2001 to 2002 US National Epidemiologic Study on Alcohol and Related Conditions (NESARC-I) showed that those with alcohol dependence had almost four times chances of having MDD than those without dependence (42). The 2012–2013 NESARC-III further indicated that those with lifetime AUD were 30% more likely to have MDD than those without AUD (4). Both moderate and severe AUD were associated with a 30% increased chance of co-occurring with MDD (41). Similarly, the comorbidity between AUD and GAD continues to generate interest. In an outpatient substance abuse clinic, nearly half of AUD patients also met criteria for current GAD, and the onset of GAD occurred prior to AUD in 67% of comorbid cases (43). In this study, the results confirmed the high comorbidity between

TABLE 7 | Factors associated with therapeutic effect on alcohol dependence by linear regression analysis ($n = 101$).

Variables	Univariate analysis				Multivariate analysis			
	B	**Beta**	***T***	***P***	***B***	**Beta**	***T***	***P***
Pre-								
Am-Fz	0.158	0.542	6.422	<0.001*	–	–	–	-
Am-Cz	0.159	0.645	8.392	<0.001*	–	–	–	–
Am-Pz	0.152	0.687	9.400	<0.001*	0.122	0.552	6.541	<0.001*
La-Fz	−0.004	−0.589	−7.256	<0.001*	–	–	–	–
La-Cz	−0.003	−0.497	−5.698	<0.001*	–	–	–	–
La-Pz	−0.003	−0.537	−6.330	<0.001*	–	–	–	–
PHQ-9	−0.037	−0.457	−5.117	<0.001*	–	–	–	–
GAD-7	−0.062	−0.548	−6.519	<0.001*	−0.027	−0.244	−2.885	0.005*
PSQI	−0.050	−0.506	−5.833	<0.001*	–	–	–	–
DSST	0.032	0.652	8.554	<0.001*	–	–	–	–

*$p < 0.05$. *Multivariate regression was analyzed using the pre-intervention variables as the independent variable and the reduction rate of AUDIT as the dependent variable by stepwise method to avoid collinearity because the independent variables were highly correlated.*

AUD and depression or anxiety symptoms, an observation that deserves more attention. However, the results were based on a hospital survey and do not represent an epidemiological population study.

After excluding the effect of age on cognitive function, the score of DSST in the AUD group was significantly lower than that of HCs, suggesting that AUD patients had cognitive impairment. The cognitive impairment indicated by the DSST test in AUD patients was confirmed also by P300 amplitudes and latency. Both P300 amplitudes and latencies of AUD patients at Fz, Cz, and Pz were attenuated below healthy controls. The clinical factors such as depression, anxiety, sleep disturbance, and cognitive impairments found in AUD in this study were consistent with other research (17, 44).

Only a few pharmacological treatments are formally available for treating AUDs. Disulfiram, naltrexone, and acamprosate are Food and Drug Administration (FDA) approved, and nalmefene is approved in European Union (45, 46). Off-label medications, such as topiramate, baclofen, gabapentin, and ondansetron, are commonly prescribed for the treatment of AUD (47, 48). As AUD is often comorbid with different neuropsychiatric disorders, antidepressants and antipsychotics are often potential alternatives. For example, recently given its effectiveness on mood, cognition, and functioning; its good safety and tolerability profile; and its low potential for abuse, vortioxetine could represent a valid pharmacological intervention in AUD-comorbid MDD patients as part of an integrated therapeutic rehabilitation program (49).

In the "Guidelines for the Diagnosis and Treatment of Mental Disorders in China (2020)" (38), benzodiazepine substitution therapy is recommended for AUD patients, especially for patients with alcohol dependence. In this study, because most AUD patients had comorbid MDD or GAD, the combination of diazepam and antidepressants was used as the main pharmacotherapy. After the 8-week pharmacotherapy, the average alcohol dose of consumption and scores of AUDIT decreased significantly, meaning that the alcohol dependence status and severity could be improved by the combination treatment. With the improvement of AUD, other symptoms, such as depression, anxiety, and sleep disturbances, also improved concurrently.

TABLE 8 | Factors associated with better therapeutic effect on alcohol dependence by binary logistic regression analysis ($n = 101$).

Variables	Univariate analysis		Multivariate analysis	
	OR	***P***	**OR**	***P***
Pre-				
Am-Fz	3.236	<0.001*	–	–
Am-Cz	7.059	<0.001*	–	–
Am-Pz	7.356	<0.001*	4.478	0.001*
La-Fz	0.959	<0.001*	–	–
La-Cz	0.967	<0.001*	–	–
La-Pz	0.969	<0.001*	–	–
PHQ-9	0.700	0.001*	–	–
GAD-7	0.575	<0.001*	–	–
PSQI	0.405	<0.001*	0.554	0.005*
DSST	1.469	<0.001*	–	–

*$p < 0.05$. *Multivariate regression was analyzed using the pre-intervention variables as the independent variable and the reduction rate of AUDIT as the dependent variable by stepwise method to avoid collinearity because the independent variables were highly correlated.*

After the 8-week pharmacotherapy, P300 amplitudes at Fz, Cz, and Pz and the score of DSST increased significantly, and P300 latencies at Fz, Cz, and Pz were significantly shorter. High reliabilities, including test–retest reliability (50), were found for the P300 amplitude and its latency in healthy monozygotic twin pairs (51) or in normal persons (52) or in treatment-naïve alcohol-dependent patients (53). Even after very prolonged abstinence, reduced P300 amplitudes were present in chronic alcoholics (54). Therefore, P300 amplitude/latency

TABLE 9 | Comparison of the ROC curves for different markers in predicting the therapeutic effect.

Variable	AUC	95%CI	Cut-off point	Se (%)	Sp (%)
Am-Fz (μV)	0.741	0.645–0.823	>8.88	88.68	47.92
Am-Cz (μV)	0.817	0.728–0.887	>8.80	66.04	85.42
Am-Pz (μV)	0.835	0.747–0.901	>8.61	71.70	79.17
La-Fz (ms)	0.761	0.665–0.840	≤420	56.60	83.30
La-Cz (ms)	0.724	0.626–0.808	≤410	41.50	95.80
La-Pz (ms)	0.750	0.654–0.831	≤413	45.28	97.92
PHQ-9 (point)	0.715	0.616–0.800	≤17	84.91	47.92
GAD-7 (point)	0.713	0.614–0.798	≤15	54.72	77.08
PSQI (point)	0.829	0.741–0.896	≤14	83.02	70.83
DSST (point)	0.807	0.717–0.879	>17	86.79	64.58

Se: The sensitivity at the cut-off point.
Sp: The specificity at the cut-off point.

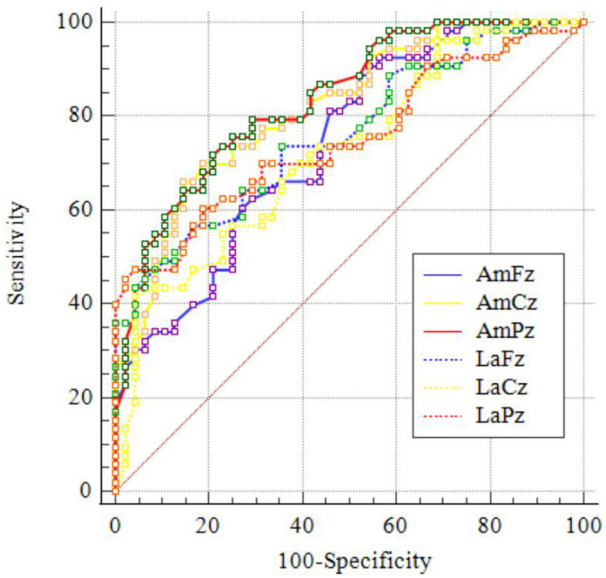

FIGURE 2 | ROC curves of the ERP data in predicting the therapeutic effect.

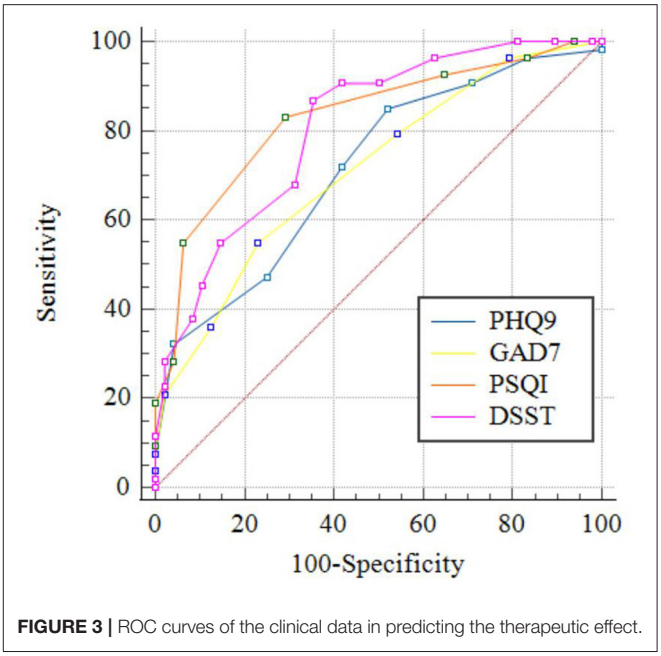

FIGURE 3 | ROC curves of the clinical data in predicting the therapeutic effect.

changes observed over the 8-week treatment period in this study are likely to reflect the effects of pharmacotherapy. However, scores of DSST; P300 amplitudes; and latencies at Fz, Cz, and Pz were still worse than those of HC, suggesting that the cognitive dysfunction of AUD patients had a partial recovery after the pharmacotherapy intervention, but the damage by alcohol to cognitive function would persist longer. Previous studies demonstrated that the P300 amplitude in AUD did not completely recover after prolonged abstinence and remained lower when compared to controls (55). The pharmacotherapy intervention was only 8 weeks in this study, so it might be that more treatment time is needed for recovery in cognitive function, if it is not at least partially irreversible. Recently, a review showed that antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, mirtazapine, and venlafaxine, are promising options for their effectiveness in reducing the craving for alcohol, weekly and monthly alcohol consumption, and in inducing marked improvements in depressive and anxiety symptoms (40). Our results support this view.

Before the pharmacotherapy intervention, both P300 amplitudes and latencies of AUD patients at Fz, Cz, and Pz correlated with average alcohol dose; drinking duration; and scores of AUDIT, PHQ-9, GAD-7, PSQI, and DSST, suggesting that the P300 amplitudes and latencies at Fz, Cz, and Pz could be used as biological markers for evaluating the clinical character and severity of AUD. After the 8-week treatment, the changes of the severity of AUD demonstrated by AUDIT scores could be predicted significantly by variables at baseline, including P300 amplitudes at Cz and Pz and scores of GAD-7, PSQI, and DSST. Jaworska et al. (20) found that normal/control-like P300 amplitudes were associated with a positive antidepressant response. Insomnia is highly prevalent in patients with AUD, and it has been related to a worse course of addiction. Patients with AUD had higher prevalence of sleep-onset insomnia (56). Patients with a moderate alcohol withdrawal syndrome also presented a lower percentage of slow-wave sleep, indicating that alcohol withdrawal syndrome severity should be considered as a critical factor for the development of non-rapid eye movement sleep alterations (57). Therefore, our results corroborate these findings from the view of pharmacotherapy intervention, indicating that P300 amplitudes at Cz and Pz, anxiety, sleep condition, and cognitive function at baseline could be used as biological markers for predicting the efficacy of treatment for AUD patients.

Interpretations from this study are limited by the sample size. Although there were 151 AUD patients recruited at baseline,

only 101 patients finished the 8-week intervention. Therefore, comparisons for therapeutic effects of pharmacotherapy intervention were made between the total subjects including drop-outs and completers by completer subsample analysis and ITT analysis, which showed no difference. Secondly, because of limited sample, we did not compare the effects of different antidepressants. Thirdly, in this study, most patients were comorbid with depression, anxiety symptoms, or insomnia, so these results could not be applied to AUD patients without such comorbidities. In addition, clinical characteristics such as depression, anxiety, sleep condition, and cognitive dysfunction were assessed by using self-rating scales by patients themselves; thus, there might be some subjective bias or recall error. The last limitation was the detection of P300. The P300 amplitude and latency at all electrodes for the target stimulus were determined automatically by the computerized program. However, it cannot demonstrate the data of non-target stimulus. So, the different score between P3 target and non-target could not be analyzed in this study.

In summary, the current study found that the P300 amplitudes and latencies at Fz, Cz, and Pz could be used as biological markers for evaluating the clinical characteristics and severity of AUD. P300 amplitudes at Cz and Pz, sleep condition, and cognitive function at baseline could be used as biological markers for predicting the efficacy of pharmacotherapy for AUD patients.

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 NTC 03910686. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CK, YP, and JYa performed data collection, data analysis, data interpretation, and manuscript preparation. JYu, CW, LW, TZ, LX, YW, and HW collected the data. XF conducted statistical analyses. All authors contributed to the article and approved the submitted version.

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Exposure to Olfactory Alcohol Cues During Non-rapid Eye Movement Sleep Did Not Decrease Craving in Patients With Alcohol Dependence

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Background and Objectives: Cue exposure therapy (CET) has been used to reduce alcohol use, but the effect of CET during sleep on alcohol dependence (AD) is unclear. The present study examined the effect of repeated exposure to an olfactory stimulus during non-rapid eye movement (NREM) sleep on cue reactivity and craving in patients with AD.

Methods: Thirty-five patients with AD were enrolled according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). All the subjects were randomly assigned to the experimental or control group. The experimental group was exposed to alcohol odor for 10 min during NREM sleep. The other group (controls) was exposed to water [control stimulus (CtrS)] for 10 min during NREM sleep. Demographic, alcohol-related, and clinical characteristics were collected at baseline. A cue-reactivity test was conducted before and after exposure to evaluate the effect of memory manipulation on acute response to an alcohol stimulus.

Results: There were no significant time × group interactions according to the visual analog scale (VAS) score of craving intensity, skin conductance response (SCR), systolic blood pressure (SBP), and diastolic blood pressure (DBP; all $p > 0.05$). Two-way ANOVA showed significant main effects of time on SCR [$F_{(1,33)} = 4.453$, $p = 0.043$], SBP [$F_{(1,33)} = 14.532$, $p = 0.001$], DBP [$F_{(1,33)} = 8.327$, $p = 0.007$], Craving-VAS [$F_{(1,33)} = 1.997$, $p = 0.167$] in two groups.

Conclusion: Exposure to olfactory alcohol cues during NREM sleep had no significant effect on alcohol craving in subjects with AD during hospitalization.

Keywords: alcohol dependence, sleep, cue exposure therapy, craving, alcohol odor

HIGHLIGHTS

- There was no significant difference between re-exposure to olfactory alcohol cues or water during NREM sleep in reducing craving and physical-reactivity to alcohol cues in subjects with alcohol dependence (AD).
- A trend toward less physiological reactivity to alcohol cues after sleep over time was observed in all subjects.
- The present study did not yield evidence of the efficacy of exposure cues during sleep in patients with AD.

INTRODUCTION

Alcohol dependence (AD) is an international public health concern (1). Globally, in 2016, 2.6% of people over 15 years of age had AD (2). Although there are many treatments for AD, including pharmacological, behavioral, and psychosocial interventions, many AD patients still experience relapse and poor quality of life because of the chronic character of this disorder, highlighting a critical need to conduct additional research to expand treatment approaches (3).

The crucial question regarding AD treatment is why patients relapse after detoxification despite a strong intention to stay abstinent. Environmental cues are major factors thought to influence behavior and modulate the risk of relapse. Hence, one increasingly dominant view in the addiction literature conceptualizes the disease as one of aberrant learning and memory (4–6). Maladaptive motivational memory (MMM) associations link conditioned stimuli (CS; e.g., people, places, or bottles) with the intoxicating and rewarding effects of unconditional stimuli (US; e.g., alcohol) (7, 8). US and CSs contribute significantly to craving and subsequent alcohol consumption behaviors (9–11). Once formed, these MMMs are difficult to resolve because they are highly robust and resistant to destabilization.

Based on the classical conditioning theory, cue exposure therapy (CET) was designed to induce memory extinction through repeated exposure to CS without alcohol consumption to decrease conditioned responses (12). Several studies have reported positive effects of CET on reduced alcohol consumption (13), reduced craving (13), prolonged abstinence, and decreased cue reactivity (14). However, in a recent meta-analysis on CET targeting alcohol use disorder (AUD), CET showed no effect on drinking-related outcomes, and CET had a moderate effect on relapse (15). There are several possible reasons for such discrepant results. Notably, memory extinction is a largely passive procedure involving exposure to environmental cues, worsening negative responses by making the subjects recall painful experiences.

A single night of aversive olfactory conditioning during non-rapid eye movement sleep (NREM) sleep stage 2 (N2) reduced cigarette consumption in smokers (16). This suggests that sleep might interfere with substance-related MMMs. In seminal works, target memory reactivation (TMR) during sleep, similar to CET during wakefulness, reduced fear responses through memory extinction and augmented the efficiency of CET (17, 18). These findings support the hypothesis that new learning during N2 sleep or slow-wave sleep (SWS) can modify memory and alter later behaviors. The TMR paradigm poses a challenge to traditional CET, as sleep induces an anesthesia-like state during which a patient's bad memory can be eliminated to optimize cognitive and behavioral therapy.

In a recent meta-analysis, the researchers found that TMR was only significant during the two NREM stages: N2 and SWS (19). Research about odor re-exposure during sleep found increased left-lateralized frontal slow spindle (11.0–13.0 Hz) and right-lateralized parietal fast spindle (13.0–15.0 Hz) activity, suggesting the possibility of a successful re-presentation of therapy-related memories during sleep (20). Specifically, during NREM sleep featuring cortical slow oscillations (SO) and thalamocortical spindles, covert memory reactivation can transform newly acquired, hippocampus-dependent learning such that neocortical representations become more stable and resistant to disruption (19). Furthermore, recent studies emphasized the importance of stage 2, spindles and the SO-spindle coupling in procedural memory consolidation (21). NREM sleep might be an excellent time window to enhance the effect of TMR. Notably, the patients with alcohol dependence have reported decreased SWS and increased latency of N2 sleep. A study indicated that N2 sleep during withdrawal accounts for 30% of total sleep time in alcohol-dependent patients, while SWS accounts for only 6.7% of total sleep time (22). Unlike healthy individuals, the reduction in sleep time might result in SWS sleep exposure alone not being able to provide stimulus exposure of sufficient duration.

Therefore, to elucidate whether repeated exposure to cues during sleep can be applied in a real clinical setting to reduce alcohol craving or consumption, we conducted a controlled study to determine the effects of re-exposure to an olfactory alcohol cue during NREM sleep in subjects with AD. Therefore, we chose to deliver odor cues at the N2 stabilization session and to continue the presentation when shifting to the N3 phase to ensure 20 min of cue exposure for extinction (23), in line with previous studies (20, 24). We hypothesized that repeated exposure to olfactory alcohol cues during NREM sleep would decrease alcohol craving and related physiological indexes in AD patients.

MATERIALS AND METHODS

Participants

All participants were recruited from psychiatric hospitals (Peking University Sixth Hospital, Beijing, and Anhui Mental Health Center, Hefei) in China. The inclusion criteria were as follows: (1) male; (2) 18–60 years old; (3) AD diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) (25) and assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (26); (4) within 14–45 days after hospital admission and not in acute clinical withdrawal from alcohol as verified by a Clinical Institute Withdrawal Assessments for Alcohol, revised version (CIWA-Ar) (27) score of <7; and (5) able to fall asleep at a regular hour according to the hospital sleep requirements. The exclusion criteria were as follows: (1) diagnosed with other Axis I psychiatric disorders and any

previous or current substance dependence other than nicotine use according to the DSM-IV; (2) significant medical conditions (e.g., cardiovascular or cerebrovascular disease); (3) dysosmia, recent (<4 weeks) nasal infection, or any self-reported difficulty with smell; or (4) use of any pharmacological treatment to reduce alcohol craving, such as acamprosate, aripiprazole, quetiapine, baclofen, or nalmefene. Written consent was obtained from all subjects before obtaining any study measurements. The study was approved by the Ethics Committee of Peking University Sixth Hospital, Beijing, China.

A total of 49 patients with AD were screened between September 2017 and December 2018. Forty-five participants were randomly assigned to two groups. The final sample consisted of 35 patients in two groups: The sleep with an olfactory alcohol stimulus (CS) group ($n = 18$) and the sleep with a water stimulus (CtrS) group ($n = 17$). The flow diagram of the enrollment process is illustrated in **Figure 1**.

Procedures

The study consisted of two main phases: (1) a baseline evaluation conducted by a professional psychiatrist during the daytime and (2) exposure to cues during sleep. Before and after exposure to the intervention, we assessed the subjective and physical responses to alcohol-related stimuli during a test with olfactory alcohol cues (test 1 and test 2). The patients in the two groups were invited to participate in baseline evaluations and cue testing (test 1). Then, all subjects were asked to participate in test 2 after sleep intervention. During the period of hospitalization, the subjects had no access to alcohol. In addition, all the subjects underwent detoxification and rehabilitation in the inpatient unit. The experimental procedures are illustrated in **Figure 2**.

Baseline Measurements

The subjects participated in an interview to obtain information about their sociodemographic, alcohol consumption-related, and clinical characteristics, including age, sex, marital status, education level, body mass index (BMI), favorite alcoholic beverage in the last year, duration of alcohol dependence, days of abstinence before baseline measurement, and daily alcohol intake (standard drinks). The Self-rating Anxiety Scale (SAS) (28) and Self-rating Depression Scale (SDS) (29) were used to assess the level of intensity of anxiety and depression during withdrawal, respectively. The Alcohol Urge Questionnaire (AUQ) (30) was used to evaluate the level of intensity of alcohol craving during the abstinent period. Sleep quality was assessed by the Pittsburgh sleep quality index (PSQI) (31). The Montreal Cognitive

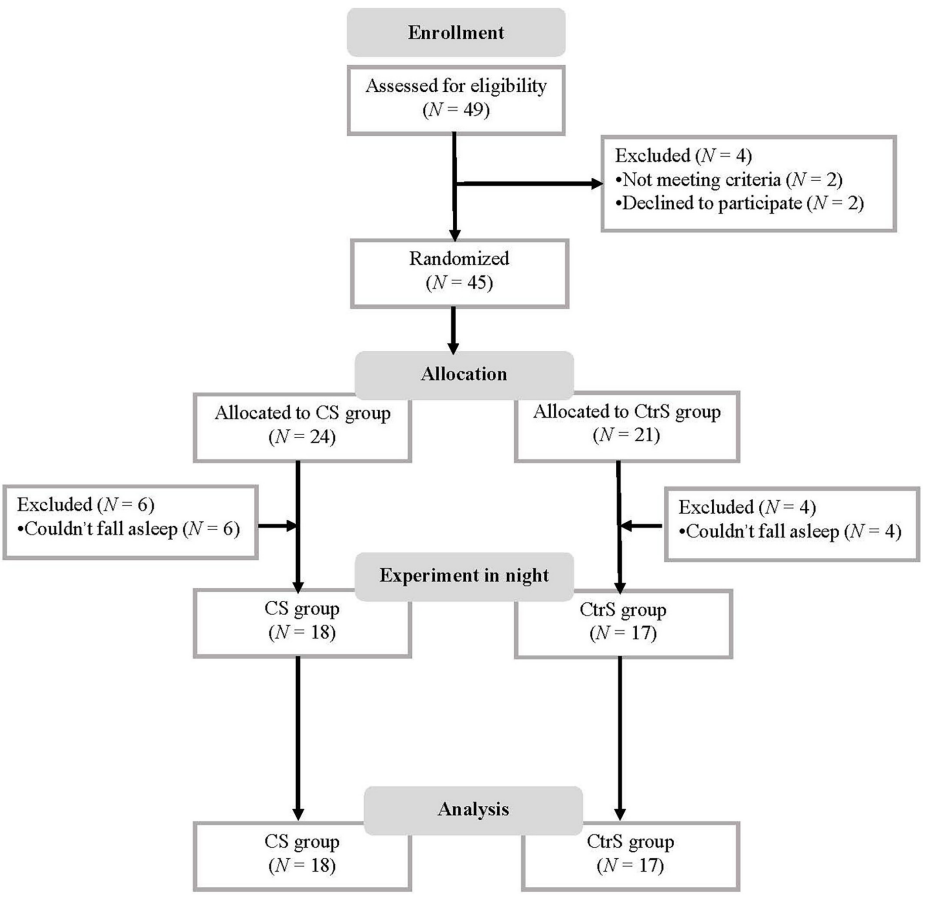

FIGURE 1 | Flow diagram. CS group, patients was re-exposed to olfactory alcohol cues; CtrS group, patients was re-exposed to water as an olfactory control.

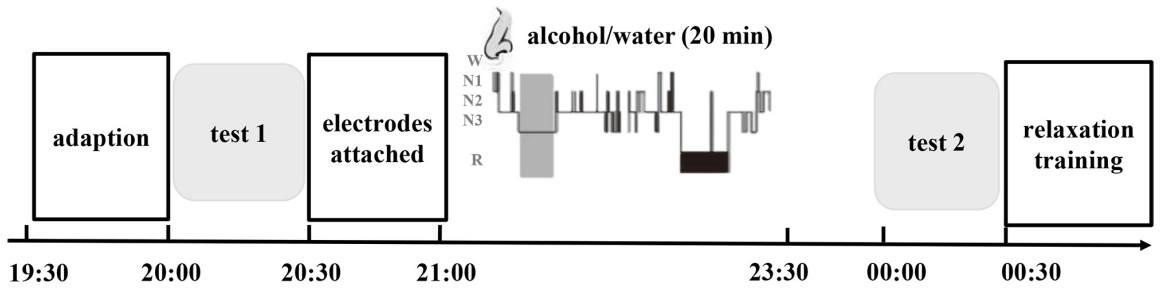

FIGURE 2 | Timeline of the experimental methods. The experimental protocol consisted of three phases: the baseline cue-reactivity test (test 1), extinction during sleep and recall test (test 2). A 2.5-h interval of nocturnal sleep between the initial test and later retesting was allowed. During the first stable NREM sleep period, one group was re-exposed to olfactory alcohol cues (CS group), and the other group was re-exposed to water as an olfactory control (CtrS group). The light gray areas represent the cue reactivity test, and the dark gray area represents the first period of NREM sleep when the odor stimulus was delivered.

Assessment (MoCA) (32) was used to evaluate cognitive function. The Fagerstrom Test for Nicotine Dependence (FTND) (33) were used to assess dependence on nicotine.

Behavioral Paradigm

In each experiment, after a break at 19:30, participants were brought to the operating room, which was maintained at 25°C. Initially, subjects were instructed to relax and adapt for 30 min. All subjects were assessed for cue reactivity (test 1) between 20:00 and 20:30 before sleep onset, and then PSG electrodes and a small nasal mask for odor delivery were applied. Because odorant stimuli are sensory cues that can be administered unobtrusively during sleep and favor subsequent extinction of maladaptive memories, we selected alcohol odor as the cue during NREM sleep (34).

To avoid the possibility of confounding effect of rapid eye movement (REM) on memory (35), we used a similar "night-half paradigm," which was deemed NREM-rich sleep (18). The subjects were allowed to sleep from 21:00 to 23:30, as well as consistent with subjects' sleep schedule during treatment. We presented the odor as soon as the online PSG recordings indicated stable N2 sleep with visible K-complexes for 2 epochs. Immediately before test 2, participants recorded their subjective alertness levels using the Stanford Sleepiness Scale (SSS) (36). Subjects were asked whether they had smelled the odor ("yes", "no," or "don't know") (37). Then, they underwent again the cue recall test, which was the same as test 1.

Cue Reactivity Assessment

All subjects were requested to evaluate the intensity of their craving on a 10-point Visual Analog Scale (VAS) ranging from 0 (not at all) to 10 (extremely high). Thereafter, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected as baseline responses. An electronic blood pressure monitor (OMRON, HBP-1300) was used to assess blood pressure. Next, the subjects were fitted with two Ag-AgCl electrodes attached to the middle phalanges of the second and third fingers of the non-dominant hand. A multichannel biofeedback device (Thought Technology Ltd., Montreal, QC, Canada, VBFB3000) was used to monitor the skin conductance response (SCR). To avoid movement artifacts, each participant was instructed to keep the hand connected to the electrodes still and relaxed; the hand rested on the arm of the testing chair throughout the whole test. A typical alcohol bottle was placed on the table directly in front of the participants; the subjects were instructed to handle and smell the alcohol bottle for 60 s without consuming it (14). The experimenters asked the participant to estimate the intensity of craving on the VAS again. The physiological measures collected included SCR and blood pressure (BP). The amplitude of the SCR to the alcohol cue was determined by calculating the peak-to-base difference within a 60 s window following the onset of odor delivery (i.e., max SCL-min SCL during exposure to alcohol cue). The baseline value was the mean SCR during the 2 s before stimulus exposure (20, 24). Successful cue-reactivity test was evidenced by increased stimulus-evoked SCR for alcohol odor cue in comparison to the baseline (17). Immediately after the test, BP was once again collected. The primary outcome measure was the change in cardiovascular response, SCR, and VAS score. All subjects underwent two cue-reactivity tests before (test 1) and after (test 2) exposure.

Polysomnographic Recordings

We used standard polysomnography (PSG) to record sleep. Electroencephalography (EEG) was performed using six scalp electrodes (C3, C4, F3, F4, O1, and O2 according to the international 10–20 system) referenced to a contralateral mastoid electrode. EEG signals were filtered between 0.3 and 35 Hz and sampled at 256 Hz. 30 s epochs were used for manual analysis. In addition to the online identification of sleep stages, EEG was scored offline according to the criteria of the American Academy of Sleep Medicine (38). Sleep stages scored include total sleep time, sleep latency, stage 1 sleep, stage 2 sleep, SWS, and REM sleep.

Olfactory Stimulus Delivery

The odorant stimulation was delivered by a respirator via a nasal mark. The alcohol odorant was diluted in purified water at a concentration of 1:50. Alcohol odors or odorless stimuli (purified water) were presented using a 30 s on/30 s off schedule for 20 min. We conducted the experiment with no instructions or information provided to the subjects regarding odor presentation during sleep. The extinction-associated odor stimulus (alcohol

odor) or odorless stimulus (water) was presented when we identified 2 consecutive N2 epochs. The odor stimulus was terminated when 20 trials (30 s on/30 s off schedule) were completed. If microarousal occurred, the stimulus that evoked the microarousal was not counted in the total number of stimuli. Presentations continued when participants transitioned into N3 but were stopped immediately upon the slightest sign of arousal, awakening, or REM sleep (24, 39). After all the subjects awakened, we asked whether they perceived the odor. Approximately 30 min after the subjects woke up or had remained awake for the same time interval, the level of sleepiness was evaluated with the SSS.

Analysis

The demographic and clinical traits, baseline craving levels, and physiological characteristics of the two groups were assessed using independent *t*-tests or chi-square tests. For measures obtained during the testing sessions, all values of the cue-reactivity tests, including the VAS score, SCR, and cardiovascular response, are presented as score changes and were calculated by subtracting the precue reactivity value from the post cue reactivity value during test 1 and test 2. These results were analyzed using repeated-measures ANOVAs, with group (CS group and CtrS group) as the between-subjects factor and time (test 1 and test 2) as the within-subjects factor. We performed *post hoc* analyses of significant effects in the ANOVAs using the Bonferroni method. Two-sided of p-values < 0.05 were considered statistically significant. Statistical analyses were carried out using SPSS version 24.0 (IBM, Armonk, NY, United States) software for Windows.

Power estimates for the current study were limited, as no studies to date have examined within-group effects of exposure to olfactory alcohol cues during sleep on reducing cue-reactivity among patients with AD. Consequently, the sample size was calculated based on a.05 alpha level, revealing that 80% power (1-β) would allow detection of a significant within-group effect of exposure observations via F-testing to assess a medium to large effect size ($0.15 \leq$ effect size $f^2 \leq 0.35$). This yielded a total required sample size of 20–90 subjects (G*power 3.1.9.2). Given these power approximations and limited resources, we estimated that our study sample of 35 individuals with repeated exposure to alcohol cues during sleep was appropriately powered to detect the hypothesized effect.

RESULTS

Demographic Characteristics

The participants comprised 35 individuals with AD, with a mean age of 38 years (SD = 7.9). There were no significant differences in demographic or alcohol-related characteristics between the two groups at baseline (all $p > 0.05$; **Table 1**).

Polysomnographic Results

Table 2 showed that re-exposure to alcohol cues or control cues during NREM sleep did not affect sleep profiles (total sleep time, $p = 0.932$; stage 1 sleep, $p = 0.143$; stage 2 sleep, $p = 0.234$; SWS, $p = 0.378$; REM sleep, $p = 0.514$; sleep efficiency, $p = 0.701$).

TABLE 1 | Demographic and clinical characteristics of the subjects in the CS and CtrS groups.

Variables	CS group (n = 18)	CtrS group (n = 17)	p-value
Age (years)	38.00 ± 5.83	38.69 ± 8.63	0.892
Education (years)	10.67 ± 3.02	12.44 ± 3.44	0.631
Marital Status			0.394
Married	13 (72.2%)	13 (76.5%)	
Single	0 (0%)	1 (5.9%)	
Divorced or widowed	5 (27.8%)	3 (17.6%)	
BMI (kg/m^2)	23.24 ± 3.40	22.91 ± 2.81	0.689
Abstinence before baseline measurement (days)	23.92 ± 8.10	21.38 ± 8.21	0.237
Duration of AD (years)	7.25 (4.25–8.75)	4.00 (3.00–5.75)	0.148
Daily alcohol intake (standard drinks)	20.90 ± 7.36	17.35 ± 6.64	0.436
Number of previous inpatient withdrawal treatments	2.00 (1.00–6.00)	2.00 (1.00–3.00)	0.833
MoCA score	26.08 ± 1.19	26.69 ± 1.89	0.551
CIWA-Ar score	1.00 (1.00–4.00)	1.50 (1.00–5.75)	0.393
PSQI score	7.25 ± 4.07	7.97 ± 3.75	0.899
FTND score	5.50 (3.25–7.00)	3.50 (1.25–5.75)	0.140
SAS score	33.33 ± 6.53	31.75 ± 6.46	0.275
SDS score	38.25 ± 11.06	36.00 ± 6.20	0.600
SSS score	3.00 (2.00–3.00)	3.00 (2.25–3.00)	0.091
Antipsychotic			
Yes	12 (66.7%)	12 (70.6%)	0.803
No	6 (33.3%)	5 (29.4%)	
Antidepressant			
Yes	14 (77.8%)	12 (70.6%)	0.627
No	4 (22.2%)	5 (29.4%)	
Sedative-hypnotic			
Yes	3 (16.7%)	2 (11.8%)	0.679
No	15 (83.3%)	15 (88.2%)	

The data are expressed as the mean ± standard deviation or median and interquartile range or frequencies. AD, alcohol dependence; BMI, body-mass index; MoCA, Montreal Cognitive Assessment; CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; PSQI, Pittsburgh Sleep Quality Index; FTND, Fagerstrom Test for Nicotine Dependence; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; SSS, Stanford Sleepiness Scale.

TABLE 2 | Sleep parameters in the CS and CtrS groups.

Variables	CS group (n = 18)	CtrS group (n = 17)	p-value
Total sleep time (min)	34.25 (24.75–50.63)	31.75 (24.63–38.13)	0.932
Sleep latency (min)	14.25 (3.13–44.63)	34.00 (19.63–48.25)	0.242
Stage 1 sleep (min)	1.25 (0.63–2.38)	0.50 (0–1.38)	0.143
Stage 2 sleep (min)	21.00 ± 8.25	16.88 ± 8.27	0.234
SWS (min)	5.25 (0.13–20.88)	12.00 (1.13–23.00)	0.378
REM sleep (min)	0 (0–1.50)	0	0.514
Sleep efficiency	0.42 ± 0.18	0.39 ± 0.13	0.701

The data are expressed as the mean ± standard deviation or median and interquartile range. SWS, slow-wave sleep; REM, rapid eye movement.

TABLE 3 | Baseline subjective and physiological indicators in the CS and CtrS groups.

Variables	CS group (n = 18)	CtrS group (n = 17)	Z	p-value
SCR mean	1.12 (0.88–1.46)	0.74 (0.47–1.43)	−1.520	0.128
SBP	137.00 (125.00–155.50)	133.00 (119.15–137.00)	−1.535	0.125
DBP	82.50 (75.25–94.25)	82.00 (67.30–90.15)	−1.023	0.306
Craving by VAS	0.30 (0–4.00)	0.20 (0–2.70)	−0.035	0.972

The data are expressed as median and interquartile range. SCR, skin conductance response, the baseline value was the mean SCR during the 2 s before stimulus exposure; SBP, systolic blood pressure; DBP, diastolic blood pressure; VAS, analog scale.

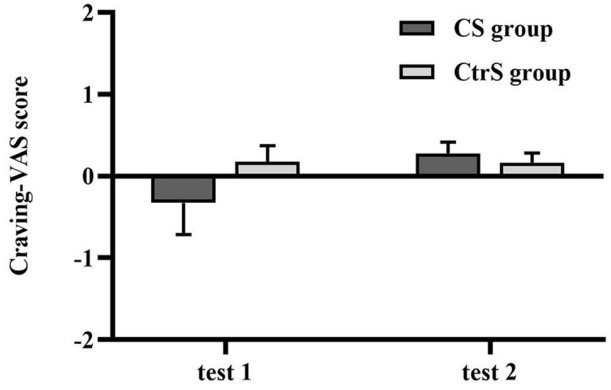

FIGURE 3 | Cue-induced alcohol craving (mean ± SEM) at baseline (test 1) and retest (test 2) for the CS group and CtrS group. These ratings were obtained from the VAS measures and were presented as change scores in craving. None of the differences were statistically significant.

No Effect of Exposure on Subjective Cue Reactivity

There was no significant difference in the craving for alcohol by VAS between the two groups at baseline (p = 0.972; **Table 3**). Despite the upward trend in craving for each group, the analysis showed no significant main effects of time [$F_{(1,33)}$ = 1.997, p = 0.167] or a group × time interaction [$F_{(1,33)}$ = 2.158, p = 0.151]. In our study, the subjects returned to baselines levels before being tested again at the second time point. The craving scores of the two cue-reactivity tests are shown in **Figure 3**.

Skin Conductance Responses Decreased in Both the Conditioned Stimuli and Control Stimuli Group

The baseline value was the mean SCR during the 2 s before stimulus exposure, and there was no significant difference in the mean SCR between the two groups at baseline (p = 0.128; **Table 3**). Regarding physiological responses to alcohol cues, repeated-measures ANOVAs, with group (CS group and CtrS group) as the between-subjects factor and time (test 1 and test 2) as the within-subjects factor, showed a significant main effect of time on SCR [$F_{(1,33)}$ = 4.453, p = 0.043], and no main effect of group [$F_{(1,33)}$ = 0.425, p = 519; **Figure 4**].

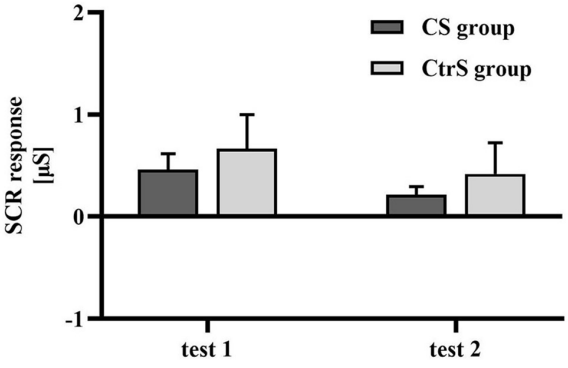

FIGURE 4 | Cue-induced SCR changes (mean ± SEM) within two cue reactivity tests for the CS group and CtrS group. SCR in both groups were significantly lower than those before intervention.

Changes in Cardiovascular Measures Over Time

There were no significant differences in the SBP and DBP between the two groups at baseline (p = 0.125 and p = 0.306, respectively; **Table 3**). However, BP was different between the two cue-reactivity tests. A main effect of time was observed for SBP [$F_{(1,33)}$ = 14.532, p = 0.001], with lower SBP in the post-exposure cue reactivity test. Similarly, a main effect of time was observed for DBP [$F_{(1,33)}$ = 8.327, p = 0.007], with lower DBP in the post-exposure cue reactivity test. However, the group × time interaction had no effect on either SBP or DBP [$F_{(1,33)}$ = 0.308, p = 0.980; $F_{(1,33)}$ = 1.069, p = 0.309; **Figures 5A,B**].

DISCUSSION

To our knowledge, this was the first study to explore the effect of re-exposure to olfactory alcohol cues during NREM sleep on alcohol craving and physiological responses in subjects with AD. We found that after sleep, repeated exposure to an alcohol stimulus during NREM sleep was ineffective in reducing subjective craving or physical responses, including changes in the SCR and blood pressure, in the CS group, contrary to our *a priori* hypothesis.

Unexpectedly, studies on memory manipulation during sleep have reported contrasting results. Because of the paucity of literature on TMR in drug users, we referred to related studies on both fear and drug memories, focusing on the effect of TMR similarly to CET. One study promoted fear extinction, in which participants underwent re-exposure to the odorant stimulus during SWS; this was more efficient than repeated exposure to cues during wakefulness (17). Another study reported re-exposure to cues during SWS reinstated fear responses in humans (24), and some animal studies also found enhanced fear responses (40, 41). Given the replication crisis in the fear memory field, recent papers have cautioned about the lack of standardization of procedures, and it is possible that the significant findings within the field of psychology are exaggerated (42). In previous human

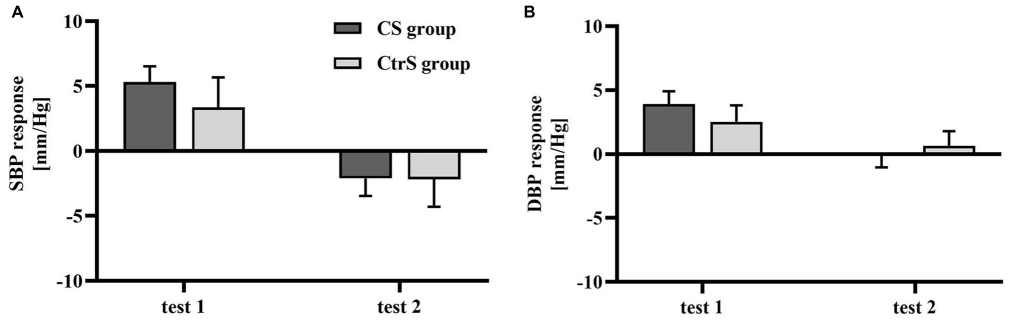

FIGURE 5 | Cue-induced cardiovascular changes within two cue reactivity tests for the CS group and CtrS group. **(A)** SBP changes. SBP responses in both groups were significantly lower than those before intervention. **(B)** DBP changes. DBP responses in both groups were significantly lower than those before intervention.

fear memory studies, fear conditioning training was conducted in healthy subjects (23), whereas our study took advantage of pre-existing addiction memory. We recruited alcohol-dependent patients in an attempt to explore the effects of TMR on maladaptive memories. However, unlike a learned fear memory, maladaptive drug-related memories are learned over hundreds of thousands of trials in multiple contexts and therefore likely to be highly resistant to destabilization and extinction (43). Moreover, memory extinction just creates a novel association between only special CS and US to compete with maladaptive alcohol memories. As a largely passive procedure, extinction training lacks reinforcement. Counterconditioning, which repairs reward cues (e.g., pictures of beer) with negative outcomes (e.g., disgust-inducing bitter liquids and odors), may provide a more powerful corrective learning experience than extinction (44). In seminal work, researchers found that olfactory aversive conditioning during N2 sleep resulted in a greater reduction in smoking behavior that lasted for a longer time than the reduction following similar conditioning in REM sleep (16). A recent study highlighted greater long-term reductions in alcohol consumption when counterconditioning was conducted following retrieval (4).

In addition, it is worth considering whether some aspect of the design might reduce the efficacy of TMR. The length of exposure is likely to influence the efficacy of extinction training. During this NREM sleep period, we delivered odor cues to participants for 20 min, resulting in each cue being presented multiple times (20 presentations). Previous research using tone cues suggested that the number of sound replays is not important for benefits of TMR to emerge (36). Furthermore, TMR benefits have been observed following the presentation of each cue only once during the sleep period (45). Some researchers have also pointed out that it is possible that amassed presentation of the cues within 3–40 min leads to extinction, whereas presenting single cues over a longer time period of 2–4 h strengthens the underlying memory trace (23).

Another possibility is the lack of sensitivity of acute laboratory assessment of the reinforcing effects of alcohol since self-reported craving might not truly reflect the urge to drink. Alcohol-related olfactory cues may be powerful appetitive cues, eliciting a craving response (34). In test 1, alcohol cues elicited strong physical reactivity but not a subjective craving increase in both groups (**Supplementary Table 1**). Participants who were re-exposed to alcohol cues or water during sleep all showed a trend toward a stronger craving for alcohol in test 2, but the difference was not significant in either group. It has been difficult to assess craving in clinical settings, and there have been inconsistent conclusions regarding the association of craving with relapse (46). We used the VAS to assess the desire for alcohol because of its ease of use in facilitating multiple evaluations of craving. VASs are easy-to-use measurement tools, but they are not as accurate as multi-item questionnaires. In comparison to multi-item questionnaires, subjects report less nuanced ratings on a unidimensional scale. Furthermore, given that craving on VAS was rated during hospitalization, when subjects were undergoing psychosocial and pharmacological treatment that may have interfered with the assessment of craving, lower VAS scores seem possible. However, to exclude the limitations of evaluating subjective craving via the VAS, we assessed the SCR and cardiovascular measures. Throughout NREM sleep, the SCR and blood pressure responses to cues both decreased over time in each group. The SCR and blood pressure showed strong generic habituation over repeated stimulus presentation. It is plausible that we found no effect of memory manipulation due to the lack of accurate measurement indexes.

Importantly, some researchers have argued that the role of individual differences has been neglected in behavior studies (10). In the context of individual differences, whether each subject can perceive cues, beyond strengthening existing associated memory, and forming new memory (i.e., memory extinction) require to expand studies. On a neural basis, hippocampal reactivation is suggested as the underlying mechanism behind consolidation during sleep. Nevertheless, little is known about the precise time course and boundary conditions of fading of hippocampal representations (47). Accordingly, the lag between learning and the posttest is also a factor that may explain the inconsistent results. To date, parametric studies on memory reactivation are lacking, and it is unclear which parameters are optimal.

There were several limitations to our study. First, the sample was relatively small, and patients were enrolled during hospitalization. Large sample size and randomized controlled studies to investigate the effect of paradigm during sleep on AD are needed in the future. The study lacked the power to

detect potential effects of re-exposure to alcohol cues during sleep. Second, in our paradigm, we did not probe the role of other sleep stages in memory (47). REM sleep is known to contribute to memory consolidation (48). In both rodent and human studies, it has been reported that REM sleep deprivation was associated with fear memory recall (49–51). Even so, a recent meta-analysis of TMR provided substantial support for the notion that TMR was not effective during REM sleep or wakefulness (19). Also, we did not explore the respective effects of N2 and SWS sleep periods on MMMs. Stimulation with learning-associated cues, mainly during SWS, has been shown to enhance declarative as well as procedural and emotional types of memory (17, 52, 53). Although the Meta-analysis reported TMR during SWS benefits on memory (19), recent work also suggested no effect of TMR on the recognition of emotionally negative or neutral memories (54). Due to the importance of stage 2, spindles and the SO-spindle coupling in memory consolidation (21), the relationship and different roles of NREM and SWS in the TMR are still unclear and need to be explored in future studies. Cue exposure might activate the addiction memory trace, leading to reduced cue response test result in the same context when tested immediately after sleep. Moreover, sleep itself might restabilize the trace during the short term. Additionally, we did not perform a similar procedure during the daytime to investigate the effect of CS exposure during wakefulness, which would determine whether the paradigm we used could prevent craving in patients with AD. Third, alcohol odor delivery was hand controlled, but the use of a respirator induced a delay in the experimenter's reaction time. Although many studies on odor cueing used a computer-controlled olfactory meter to deliver odor, it was challenging to persuade clinicians to use the machine in real clinical settings. These limitations could be overcome in the future. Finally, our sample comprised only men. Therefore, the generalization of our conclusions to female patients with AD is limited. As previous studies have shown that cue-induced alcohol craving and physiological cue reactivity are associated with alcohol relapse risk and that well-tolerated re-exposure to cues during sleep could facilitate extinction memory, the hypothesis in the current study requires further testing to evaluate effects on alcohol craving and improve treatment outcomes.

CONCLUSION

To our knowledge, the present study is the first to examine the effect of CS re-exposure during NREM sleep on addiction memory in individuals with AD. We observed no impact of re-exposure to alcohol cues during NREM sleep on cue-induced craving and physiological response. The replication crisis in psychology highlights the need for further examination of factors that may moderate memory extinction manipulation effects and the lack of standardized procedures.

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 the Ethics Committee of Peking University Sixth Hospital, Beijing, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RZ, ZN, RT, YX, YM, WS, JD, and HS contributed to the study conception and design. RZ, SZ, JC, and LP evaluated all the patients, performed the data collection, and conducted the study. YZ and WS conducted the sleep data scoring. RZ and JD performed the data analyses. RZ drafted the manuscript. LL and HS critically revised the important intellectual content in the manuscript. JD and HS were in charge of supervision. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.837573/full#supplementary-material

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The Effect of the Non-compressed Oxygen Therapy and Hyperbaric Oxygenation in Combination With Standardized Drug Therapy on the Blood Acid-Base State Biomarkers in Alcohol Withdrawal Syndrome, an Experimental Study

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In alcohol withdrawal syndrome (AWS), pathophysiological mechanisms cover acid-base disturbances that affect the clinical picture of this state. An earlier study found that oxygen therapy methods in combination with pharmacotherapy improved the cognitive state in persons suffering from AWS. As impairments in the acid-base state influence the general health, timely and effective correction of these acid-base disturbances could result in a potential improvement in the treatment of the alcohol withdrawal symptoms. Therefore, the aim of this study was to evaluate the effectiveness of non-compressed oxygen therapy (NOT) and hyperbaric oxygenation (HBO) in combination with standard drug therapy (SDT), based on the dynamics of the acid-base state (ABS) in blood during AWS. HBO is the use of oxygen under pressure, whereas NOT uses oxygen without pressure. A comparative assessment of the acid-base state biomarkers was made in 160 patients with a moderate alcohol withdrawal state (3 groups), namely, in patients who underwent SDT only (control group/CG; $n = 42$) and two comparison groups who underwent SDT in combination with NOT (SG1 group; $n = 56$) and HBO (SG2 group; $n = 62$). The use of both oxygen therapy methods (i.e., NOT and HBO) in combination with SDT corrected the ABS in a shorter time and more effectively, which was due to the better restoration of the carbonate buffer system. Although we did not find proof that novel oxygen-related therapeutic procedures such as NOT and HBO in combination with SDT improved the alcohol withdrawal symptoms, it helped with the faster restoration of the acid-base state.

Keywords: alcohol withdrawal syndrome, acid-base, markers, hyperbaric oxygenation, treatment, non-compressed oxygen therapy

INTRODUCTION

Alcohol withdrawal syndrome (AWS) is a result of the several pathophysiological mechanisms. After a sharp cessation of alcohol consumption, the inhibitory effect of ethanol on the central nervous system ends, which leads to an increase in the excitatory effect of glutamate and changes in neurotransmitter systems (1–4). In AWS, there are disturbances in energy homeostasis and a decrease in brain tissue reserves, which seems to be partly due to deregulated brain metabolism (3, 5).

Active transmembrane electrolyte transport is one of the most important components of the energy-dependent process. Inorganic electrolytes provide up to 96% of the total osmotic pressure of blood (5, 6). The electrochemical balance of ions between the outer and inner layer of the membrane creates its potential. Energy potential of cells is based on the universal process of glucose breakdown, but with a lack of oxygen in cells of the body, accumulation of lactate begins, which is a toxic substance. As a result, lactic acidosis develops, causing the dysfunction of many cells, primarily nerve and muscle cells (6–9). It was found that, with AWS, the body's need for oxygen increases, which decreases with the decline in the severity of clinical symptoms (5). In AWS, oxygen deficiency is predominantly of the tissue type, as evidenced by the low arteriovenous oxygen difference. Presumably, this may be due to the effect of alcohol breakdown products on the dehydrogenase system, which subsequently causes cerebral tissue hypoxia with subsequent disturbances in the mental sphere (6).

Patients with alcohol dependence (AD) syndrome have lower serum concentrations of potassium, magnesium, bicarbonate, calcium, and phosphate as well as a lower arterial pH. The severity of AWS correlates with the dynamics of the ABS markers, circulating blood volume, and water-electrolyte balance. Also with AWS, disturbances in homeostasis may occur with acidosis or alkalosis. The causes of the ABS disturbances can be respiratory, metabolic, or a combination of both. Acidosis is a deviation of ABS, characterized by an excessive content of acid anions in the blood and tissues with a decrease in pH (9–13).

Alcohol withdrawal syndrome of any severity requires mandatory treatment for the prevention of severe complications as epileptic seizures, Wernicke encephalopathy or dementia, and the treatment of already developed disorders as malnutrition or electrolyte and acid-base imbalance (13). For a successful treatment of AWS, in addition to relieving psychopathological, somato-neurological, and autonomic symptoms, it is desirable to replenish the fluid deficit, to correct water-electrolyte disorders and acid-base disorders (13). The use of standard treatment for AWS, which contains predominantly psychotropic drugs, does not always take into account changes in the ABS, especially in moderate AWS, when medical care is provided mainly outside of intensive care units.

Hyperbaric oxygen (HBO) therapy involves the use of oxygen under pressure to facilitate tissue healing and has been used routinely for over 40 years in the medicine. Currently, HBO is a well-established therapy for several pathological states including air or gas embolism, carbon monoxide poisoning, decompression sickness, and wounds/soft tissue infections (14). Tissue oxygen disturbances and cell dysfunctions/degenerations are also considered as the etiology of neuropsychiatric disorders, e.g., post-traumatic stress disorder, major depression, traumatic brain injury, or autism spectrum disorder, as a target of HBO (14, 15).

As disturbances in ABS can influence overall health (16), we hypothesized that methods of oxygen therapy can also be one of additional methods that positively affect ABS disturbances during the AWS, which potentially can improve AWS. The effect of oxygen therapy on ABS in persons suffering from AWS has not been studied so far. Biochemical parameters such as pH, carbon dioxide tension, bicarbonate, Cl–, lactate, and blood base excess (BE) are called acid-base markers (16). Therefore, the aim of this study was to evaluate the effectiveness of HBO and non-compressed oxygen therapy (NOT) methods in combination with standard drug therapy (SDT) on the dynamics of biological markers of ABS during AWS. The NOT group was used to compare the effect of hyperbaric with uncompressed oxygenation.

MATERIALS AND METHODS

Participants

A total of 160 male patients with moderate AWS were examined. The study group was recruited from people successively admitted to the hospital for the treatment of the AWS. All of the patients suffered from AD and were inpatients receiving treatment at the Republican Scientific and Practical Center for Mental Health in Belarus: 62 people underwent HBO (SG2) and 56 NOT (SG1) together with SDT and 42 underwent only SDT in accordance with the protocols of medical help (CG). Biochemical analyses were carried out on the 1st, 3rd, and 7th day of the treatment.

The most recent alcohol consumption of the subjects took place the day before admission to inpatient treatment. Clinical examination of the somatic status was carried out according to the generally accepted scheme. The exclusion criteria were the presence of chronic diseases that might influence ABS biomarkers or contraindications in the HBO: non-alcoholic liver disease, acute and chronic pancreatitis, chronic renal failure, viral hepatitis, metabolic diseases (diabetes), obstruction of the Eustachian tubes, increased body temperature, epilepsy, claustrophobia, oncological diseases, acute inflammatory processes, severe cardiovascular disease, bleeding and trauma, and addiction to psychoactive substances other than ethanol.

For the SDT treatment of the AWS, parenterally and orally, diazepam was used, in a dose not exceeding 40 mg/day. In addition, intravenous natrium chloratum injections, multielectrolyte fluids, and glucose were used. In the HBO group, the patients received an HBO session one time a day for 7 days. The pressure in the HBO chamber reached 0.2 MPa (2.0 ATA) and lasted 30 min. At the end of treatment, the pressure gradually decreased over a period of 10–15 min. The patients in the NOT group were, similarly to HBO, put into an HBO chamber one time a day for 7 days, but the NOT patients received oxygen without pressure for the same time period.

Ethical Issues

The study was approved by the local Bioethical Committee of Belarusian State Medical University (N 8/124.15.08.2017) and conducted in accordance with the Helsinki Declaration. Informed written consent was obtained from all the subjects after explaining the nature, purpose, and potential risks of the study.

Procedures

Data and Sample Collection

To assess the severity of AWS symptoms, Clinical Institute for Withdrawal Assessment-for Alcohol (CIWA-A) scale was used (17). In patients of all the study groups at the time of the first medical intervention, the CIWA scores were in the range of 16–20 points (no statistical differences), which corresponded to moderate AWS and was one of the significant criteria for inclusion in the study.

Clinical verification and diagnosis of AD were carried out by qualified specialists in accordance with the diagnostic (research) criteria of International Classification of Diseases (ICD)-10 (18) (presence of at least 3 out of 6 criteria for AD, observed within 1 month or periodically repeated within 12 months, objectified by two independent sources) and indicators >20 points on the Alcohol Use Disorders Identification Test (AUDIT) (19).

The study of anamnestic data, including the previous features of the course of disease, assessment of the quality, and effectiveness of the clinical dynamics of AWS, was carried out by using the Belarusian index of severity of addiction for clinical use and training ("B-ITA," version 2.3-3.01.2001) and "scales of dynamics of psychopathological disorders in AWS, post-withdrawal state, remission" (6, 20). The dynamics of the clinical symptoms of AWS were assessed every day from the first day of admission in the hospital.

Analytical Methods

The biochemical study included an assessment of blood ABS with the analysis of its most relevant components: pH, partial pressure of carbon dioxide oxygen in the blood (i.e., pCO_2 and pO_2), saturation (i.e., SO_2), levels of hemoglobin, glucose, Ca^{++}, Na^{+}, actual bicarbonate (HCO^{3-}), extracellular fluid base excess/base excess (BEecf), blood base excess/actual base excess (BEb), standard bicarbonate (SB), total blood oxygen concentration (O_2Ct), oxygenation (O_2Cap), and alveolar-arterial gradient ($D(A\text{-}a)O_2$). The abovementioned parameters were determined by using the routine laboratory methods on the Osmotech OPTI Blood Gas Analyzer. ABS biomarkers were evaluated on the 1st, 3rd, and 7th day of the treatment.

Statistical Analysis

Statistical processing of the research results was carried out by using the statistical software package STATISTICA 10.0 (SN: BXXR207F383502FA-D). To assess the normality of distribution, the Kolmogorov-Smirnov test was used. Taking into account the normality of the distribution, the methods of parametric statistics were used. A comparison of the mean values between groups was carried out by using one-way analysis of variance (ANOVA with *post-hoc* tests) and within the group (between 1st, 2nd, and 7th day-dependent variables) by using the *t*-test. A comparison of the groups by a qualitative binary feature was carried out by using the χ^2 criterion, and the odds ratio was calculated. A mixed design ANOVA (3 time-points response × 3 groups) was used to test the differences in acid-base disturbances over the course of the 1st, 3rd, and 7th day of treatment between the SG1 (1), SG2 (2), and CG (3) groups. The differences between groups were considered significant at $p < 0.05$.

RESULTS

The average age of the patients in study groups did not differ significantly between them and was, respectively: 38.3 ± 1.3 years in SG1; 40.2 ± 1.3 years in SG2; and 38.8 ± 1.3 years in CG. Participants were from rural (39.7%) and urban (60.3%) areas. The educational level was secondary (30.6%), secondary specialized (56.5%), and higher (12.9%). There were no statistically significant differences between the groups in the time of nicotine dependence and number of smoked cigarettes per day (from 94 to 97% were smokers). The time of AD in the groups was: in CG, 17.6 ± 2.2 years; in SG2, 20.9 ± 2.6 years; and in SG1, 16.5 ± 2.1 years (mean ± SD). The average duration of the most recent chronic alcohol drinking period was: in the control group, 14.6 ± 1.7 days; in SG2, 14.6 ± 1.7 days; and in SG1, 13.5 ± 2.3 days, with no statistical differences.

The analysis of the levels of blood ABS indicators presented in **Table 1** showed that most of them (except of glucose and Na^{+}) underwent significant changes during the treatment. Some of these indicators for most of the subjects were within the range of standard values. The data were analyzed in two ways, namely, within-group and between-group differences.

Although 7 days of therapy in groups with oxygen methods (i.e., NOT and HBO) significantly changed the pH values, its levels did not differ significantly for more than +0.1 from the normal range.

In addition to the main ABS indicators (**Table 1**), **Table 2** presents indicators that show mainly compensatory resources and the capabilities of the body in certain biochemical disorders. The average levels of bicarbonate (HCO^{3-}) in all the groups are higher than the reference ranges (7.35–7.45). Although we found a significant difference during the 7-day period (within-group) of AWS only in HCO_3 in the CG group (**Table 2**), we found statistical differences between groups in all the parameters at all the time points of the study.

The results with changes in the ABS parameters that are the most important to the discussion are presented in **Figure 1**.

Table 3 shows that only CO_2 values had significant effect for time, groups, and a significant time-by-group interaction but without statistical significance of changes in time in the *t*-test (**Table 1**). Mixed ANOVA design also showed significant interactions for time and groups in pH and O_2Ct values with a strong tendency to significant time-by-group interaction (O_2Ct values without significant changes in time in the *t*-test, **Table 1**). The effect for time in pH value had a higher effect size than for groups. It was also found a significant effect of only time for Na^{+} and a significant effect of only group for pO_2, SO_2, glucose, Ca^{2+}, and HCO^{3-}. The significant effect of time and group but without

TABLE 1 | The dynamic changes of blood acid-base parameters.

Index	Groups			*P*
	SG1 (1)	SG2 (2)	CG (3)	
pH after 1 day of therapy	7.505 ± 0.007	7.522 ± 0.007	7.536 ± 0.005	$P_{1,2-3} < 0.05$
pH after 3 days of therapy	7.499 ± 0.006	7.503 ± 0.005	7.513 ± 0.004	$P_{1,2-3} < 0.05$
pH after 7 days of therapy	7.484 ± 0.005	7.481 ± 0.006	7.507 ± 0.003	$P_{1,2-3} < 0.05$
pCO_2 after 1 day of therapy (mmHg)	38.09 ± 0.72	39.23 ± 0.90	35.44 ± 0.83	$P_{1,2-3} < 0.05$
pCO_2 after 3 days of therapy (mmHg)	38.97 ± 0.79	39.83 ± 1.03	35.90 ± 0.91	$P_{1,2-3} < 0.05$
pCO_2 after 7 days of therapy (mmHg)	40.22 ± 0.88	38.92 ± 0.85	36.07 ± 0.95	$P_{1,2-3} < 0.05$
pO_2 after 1 day of therapy (mmHg)	74.61 ± 1.68	80.63 ± 1.53	73.23 ± 2.02	$P_{2-1,3} < 0.05$
pO_2 after 3 days of therapy (mmHg)	78.38 ± 1.38	82.62 ± 2.00	71.59 ± 1.73	$P_{1,2-3} < 0.05$
pO_2 after 7 days of therapy (mmHg)	78.82 ± 1.39	82.42 ± 1.73	70.36 ± 2.67	$P_{1,2-3} < 0.05$
SO_2 after 1 day of therapy (%)	96.76 ± 0.19	97.37 ± 0.26	94.17 ± 1.37	$P_{1,2-3} < 0.05$
SO_2 after 3 days of therapy (%)	96.45 ± 0.31	97.23 ± 0.34	95.07 ± 0.39	$P_{1,2-3} < 0.05$
SO_2 after 7 days of therapy (%)	96.56 ± 0.31	97.46 ± 0.30	94.92 ± 0.45	$P_{1,2-3} < 0.05$
Hemoglobin after 1 day of therapy, g/l	148.4 ± 1.73	156.2 ± 1.75	155.4 ± 1.99	$P_{1-2,3} < 0.05$
Hemoglobin after 3 days of therapy, g/l	143.9 ± 1.91	154.7 ± 2.06	150.6 ± 1.98	$P_{1-2,3} < 0.05$
Hemoglobin after 7 days of therapy, g/l	143.3 ± 1.73	152.6 ± 1.93	148.2 ± 1.96	$P_{1-2,3} < 0.05$
Ca^{++} after 1 day of therapy, mmol/l	1.00 ± 0.02	0.98 ± 0.02	0.89 ± 0.02	$P_{1,2-3} < 0.05$
Ca^{++} after 3 days of therapy, mmol/l	1.01 ± 0.01	0.99 ± 0.02	0.90 ± 0.02	$P_{1,2-3} < 0.05$
Ca^{++} after 7 days of therapy, mmol/l	1.00 ± 0.01	1.00 ± 0.02	0.93 ± 0.01	$P_{1,2-3} < 0.05$

pH, Potential of hydrogen; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SO_2, oxygen saturation; SDT, level of hemoglobin, glucose, and Ca^{2+} and Na^+ in the blood of persons suffering from an alcohol withdrawal state (AWS) that had standardized drug therapy; NOT, non-compressed oxygen therapy; HBO, hyperbaric oxygenation; CG, patients who underwent SDT only (control group); SG1, patients who underwent SDT in combination with NOT; SG2, patients who underwent SDT in combination with HBO; P1, 2, −3 < 0.05 means statistically significant difference between the SG1 (1) and CG (3) groups, statistical difference between SG2 (2) and CG(3) groups, and no differences between the SG1 (1) and SG2 (2) groups; P2–1, 3 < 0.05 means statistically significant difference between the SG1 (1) and SG2 (2) groups, statistical difference between CG(3) and SG2 (2) groups, and no differences between the SG1 (1) and CG (3) groups; P1–2, 3 < 0.05 means statistically significant difference between the SG1 (1) and SG2 (2) groups, statistical difference between SG1 (1) and CG(3) groups, and no differences between the SG2 (2) and CG (3) groups; p < 0.05 at the bottom of each group means statistically significant difference in parameter during the 7-day treatment period. There were found intragroup differences only in the pH values in SG1, SG2, and CG groups.

significant time-by-group interaction was found for hemoglobin, BEecf, BEb, SB, O_2Cap, and D(a-A)O_2.

Supplementary Table 1 shows the differences in the distribution of subjects (%) with the blood levels of the main indicators of ABS deviating from the reference ranges, in the GS1, GS2, and the CG groups. Statistically significant between-group differences from the reference ranges were found in pCO_2, pO_2, and SO_2 but not for pH, hemoglobin, glucose, Ca^{2+}, and Na^+ values. Statistical within-group differences were located only for the number of persons (%) with indicators $pO_2 < N$.

In groups where the methods of oxygen therapy were used, compared with CG, the number of subjects with low pO_2 values decreased significantly.

The levels of ionized sodium (Na^+) were within the reference ranges in the vast majority of subjects in all the groups, and the applied methods of treatment did not have a significant effect on this indicator.

The data in **Supplementary Table 2** show statistically significant higher relative numbers of persons in SG1 and SG2, compared with the CG, with higher levels of HCO^{3-}, BEecf, BEb, and SB and lower levels of D(A-a)O_2 than the reference ranges. For parameters, such as HCO^{3-} and BEecf, this is relevant from the third day from the start of therapy, and for the rest, from the first day. **Supplementary Table 2** also shows the most relevant components of the ABS, which are more actively involved in the process of the normalization of ABS.

We found no statistically significant differences between the groups or within groups in the CIWA-A scores (all the values were in the 16–20 point range) and no correlations between the CIWA-A scores and ABS markers.

DISCUSSION

Evidence of the positive influence of oxygen therapy methods on cognitive functions during the AWS can be found in the medical literature (1). As we hypothesized, our study showed the positive influence of oxygen therapy methods on the markers of the ABS.

Our results demonstrate that by the seventh day of therapy in groups with the oxygen therapy methods used in the complex treatment, the results of the pH levels did not differ significantly from the results exceeding the norm by +0.1. The pH index on the seventh day of therapy shows that in the SG1 and SG2 groups, there were phenomena of subcompensated alkalosis, which was not observed in CG (**Figure 1**, **Table 1**). One of the significant markers of ABS is the pH indicator (9), which represents the negative decimal logarithm of the molar concentration of hydrogen ions in cells and biological fluids. This component is one of the most important parameters for ensuring the

TABLE 2 | The dynamic changes of the acid-base state parameters.

Index	Groups			*P*
	GS1 (1)	GS2 (2)	CG (3)	
HCO_3- after 1 day of therapy, mmol/l	32.08 ± 0.73	32.28 ± 0. 71	28.23 ± 0.68	$P_{1,2-3} < 0.05$
HCO_3- after 3 days of therapy, mmol/l	31.55 ± 0.52	31.16 ± 0.72	27.63 ± 0.76	$P_{1,2-3} < 0.05$
HCO_3- after 7 days of therapy, mmol/l	31.67 ± 0.59	31.57 ± 0. 71	27.17 ± 0.71	$P_{1,2-3} < 0.05$
BEecf after 1 day of therapy, mmol/l	9.87 ± 0.59	9.08 ± 0.76	4.92 ± 0.73	$P_{1,2-3} < 0.05$
BEecf after 3 days of therapy, mmol/l	9.87 ± 0.59	9.08 ± 0.76	4.92 ± 0.73	$P_{1,2-3} < 0.05$
BEecf after 7 days of therapy, mmol/l	8.55 ± 0.52	8.19 ± 0.74	3.49 ± 0.74	$P_{1,2-3} < 0.05$
BEb after 1 day of therapy, mmol/l	9.86 ± 0.48	9.26 ± 0.61	5.83 ± 0.61	$P_{1,2-3} < 0.05$
BEb after 3 days of therapy, mmol/l	8.58 ± 0.42	7.96 ± 0.61	4.63 ± 0.66	$P_{1,2-3} < 0.05$
BEb after 7 days of therapy, mmol/l	8.59 ± 0.41	8.38 ± 0.58	4.32 ± 0.62	$P_{1,2-3} < 0.05$
SB after 1 day of therapy, mmol/l	33.69 ± 0.48	33.15 ± 0.62	29.62 ± 0.59	$P_{1,2-3} < 0.05$
SB after 3 days of therapy, mmol/l	31.80 ± 0.67	31.83 ± 0.59	28.53 ± 0.63	$P_{1,2-3} < 0.05$
SB after 7 days of therapy, mmol/l	32.37 ± 0.39	32.26 ± 0.57	28.11 ± 0.63	$P_{1,2-3} < 0.05$
O_2Ct after 1 day of therapy, ml/dl	20.20 ± 0.24	21.41 ± 0.26	20.76 ± 0.30	$P_{2-1,3} < 0.05$
O_2Ct after 3 days of therapy, ml/dl	19.65 ± 0.39	21.15 ± 0.31	20.76 ± 0.30	$P_{2-1,3} < 0.05$
O_2Ct after 7 days of therapy, ml/dl	19.48 ± 0.25	20.93 ± 0.28	19.77 ± 0.26	$P_{2-1,3} < 0.05$
O_2Cap after 1 day of therapy, ml /dl	20.63 ± 0.24	21.71 ± 0.24	21.51 ± 0.30	$P_{1-2,3} < 0.05$
O_2Cap after 3 days of therapy, ml/dl	20.01 ± 0.27	21.47 ± 0.29	20.93 ± 0.27	$P_{1-2,3} < 0.05$
O_2Cap after 7 days of therapy, ml/dl	19.92 ± 0.24	21.19 ± 0.26	20.56 ± 0.27	$P_{1-2,3} < 0.05$
D(A-a)O_2 after 1 day of therapy (mmHg)	23.28 ± 1.44	20.35 ± 1.72	30.32 ± 1.85	$P_{1,2-3} < 0.05$
D(A-a)O_2 after 3 days of therapy (mmHg)	21.62 ± 1.33	17.93 ± 1.91	30.49 ± 1.88	$P_{1,2-3} < 0.05$
D(A-a)O_2 after 7 days of therapy (mmHg)	19.49 ± 1.46	18.01 ± 1.84	29.19 ± 1.94	$P_{1,2-3} < 0.05$

HCO_3, bicarbonate level; BEecf, extracellular fluid base excess/base excess; BEb, blood base excess/actual base excess; SB, standard bicarbonate; O_2Ct, oxygen concentration; O_2Cap, total blood oxygenation; SDT, alveolar-arterial gradient (D(A-a)O_2) in the blood of persons suffering from alcohol withdrawal state (AWS) that had standardized drug therapy; NOT, non-compressed oxygen therapy; HBO, hyperbaric oxygenation; CG, patients who underwent SDT only (control group); SG1, patients who underwent SDT in combination with NOT; SG2, patients who underwent SDT in combination with HBO; P1, 2, −3 < 0.05 means statistically significant difference between the SG1 (1) and CG(3) groups, statistical difference between the SG2 (2) and CG(3) groups, and no differences between the SG1 (1) and SG2 (2) groups; P2–1, 3 < 0.05 means statistically significant difference between the SG1 (1) and SG2 (2) groups, statistical difference between CG(3) and SG2 (2) groups, and no differences between the SG1 (1) and CG (3) groups; P1–2, 3 < 0.05 means statistically significant difference between the SG1 (1) and SG2 (2) groups, statistical difference between the SG1 (1) and CG(3) groups, and no differences between the SG2 (2) and CG (3) groups; p < 0.05 at the bottom of each group means statistically significant difference in the parameters during the 7-day treatment period. There were found intragroup differences only in the HCO^{3-} values in the CG group.

homeostasis of the body. The bicarbonate (hydrocarbonate) buffer system is a kind of compensatory reserve resource that ensures the normalization of homeostatic equilibrium in moderate AWS of persons with AD (9). A shift in pH in the range of ±0.1 causes respiratory and circulatory disorders, ± 0.3 disturbances in hemodynamics and ventilation of the lungs, more than ± 0.4 leads to the death of the body (9, 11, 18). In arterial blood (plasma), pH ranges within 7.40 ± 0.04. All violations of ABS with the shift in the concentration of hydrogen ions are divided into acidosis and alkalosis: acidosis at pH < 7.4; alkalosis at pH > 7.4 (4, 6, 9). Therefore, subjects without oxygenation procedures (i.e., CG) might have higher circulatory disturbances at the level of decompensated alkalosis than in the SG1 and SG2 groups.

When analyzing the pH indicator, we noticed that subjects with moderate AWS had alkalosis phenomenon (**Figure 1**, **Table 1**). Given that the group mean pH values were >7.5, according to **Supplementary Table 1**, the vast majority of subjects had higher HCO^{3-} levels than the normal/reference ranges (N), with pCO_2 levels close to normal or low (**Table 1** and **Supplementary Table 1**). In these cases, it indicates the metabolic alkalosis. pH values higher than 7.5 indicate decompensated alkalosis. In all the groups, there was a statistically significant decrease in pH levels toward the normalization of this indicator, especially in groups with supplemented methods of oxygen therapy (i.e., NOT and HBO). Moreover, the advantages of any method of oxygen therapy used in the complex treatment have not been established over each other. Metabolic alkalosis is a primary disorder of the ABS, in which the level of HCO^{3-} rises, pH is higher than 7.45, and CO_2 decreases or is normal. The primary mechanism for the shift in equilibrium in metabolic alkalosis is the loss of non-volatile acids by the body or excessive introduction of bases into the body. Clinically, such biochemical disorders can be accompanied by changes in consciousness, muscle weakness, hyporeflexia, polyuria, polydipsia, and myocardial dysfunctions (9). The use of SDT alone as well as its combination with methods of oxygen therapy did not allow for the normalization of HCO^{3-} levels, but some tendencies in the process of normalization occurred. Normalization would probably require a longer treatment period of our study. The use of oxygen therapy methods in complex treatment also reduced the number of persons with

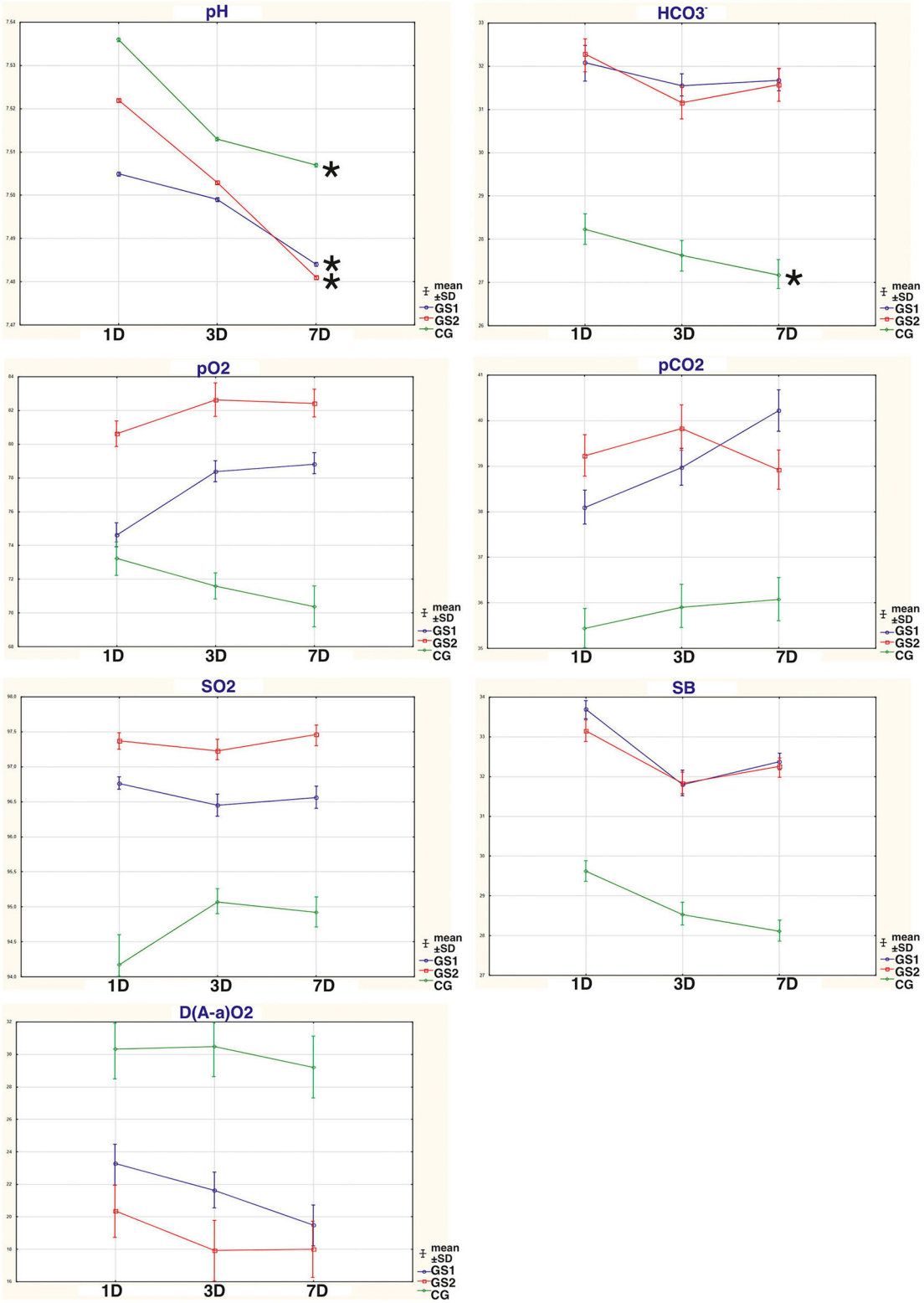

FIGURE 1 | The dynamic changes in the acid-base parameters that are most important to the discussion: pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), oxygen saturation (SO_2), bicarbonate level (HCO_3), standard bicarbonate (SB), and alveolar-arterial gradient ($D(A\text{-}a)O_2$), in the blood of persons suffering from AWS that had standardized drug therapy (SDT), non-compressed oxygen therapy (NOT), and hyperbaric oxygenation (HBO); CG, patients who underwent SDT only (control group); SG1, patients who underwent SDT in combination with NOT; SG2, patients who underwent SDT in combination with HBO; 1D, first day of therapy; 3D, third day of therapy; 7D, seventh day of therapy; *significant differences within the group $p < 0.05$ (*t*-test).

TABLE 3 | Summary of the blood acid-base state results obtained in the mixed design analysis of variance (ANOVA) with repeated measures.

Index in 1_7 days of therapy in GS1, GS2 and CG groups		Mixed Design ANOVA with repeated measures			
		F	**df**	η^2	***P***
pH effects	For time	18.0	2	0.141	**<0.0001*** **
	For group	0.02	2	0.125	**0.0006*** **
	For interaction: time+ group	2.0	4	0.039	0.065
pCO_2 effects	For time	4.0	2	0.035	**0.019***
	for group	3.8	2	0.064	**0.024***
	For interaction: time+ group	2.5	4	0.044	**0.037***
pO_2 effects	For time	1.1	2	0.010	0.325
	For group	9.1	2	0.142	**0.0002*** **
	For interaction: time+ group	1.7	4	0.030	0.150
SO_2 effects	For time	0.5	2	0.004	0.613
	For group	11.6	2	0.172	**<0.0001*** **
	For interaction: time+ group	1.0	4	0.016	0.432
Hemoglobin effects	for time	10.7	2	0.088	**<0.0001*** **
	For group	9.0	2	0.140	**0.0002*** **
	For interaction: time+ group	1.4	4	0.025	0.213
Glucose effects	for time	0.9	2	0.006	0.400
	For group	3.1	2	0.043	**0.047***
	For interaction: time+ group	1.6	4	0.023	0.158
Ca^{++} effects	For time	1.2	2	0.010	0.294
	for group	8.1	2	0.128	**0.0004*** **
	For interaction: time+ group	0.6	4	0.011	0.648
Na^{+} effects	For time	4.5	2	0.039	**0.011***
	For group	2.1	2	0.036	0.126
	for interaction: time+ group	0.6	4	0.009	0.693
HCO_3- effects	For time	1.9	2	0.017	0.142
	For group	10.3	2	0.158	**<0.0001*** **
	For interaction: time+ group	0.2	4	0.005	0.883
BEecf effects	For time	6.5	2	0.056	**0.001** **
	For group	14.4	2	0.207	**<0.0001*** **
	For interaction: time+ group	0.5	4	0.009	0.720
BEb effects	For time	10.7	2	0.089	**<0.0001*** **
	For group	15.4	2	0.219	**<0.0001*** **
	For interaction: time+ group	0.7	4	0.012	0.576
SB effects	For time	7.7	2	0.065	**0.0005*** **
	for group	13.7	2	0.199	**<0.0001*** **
	For interaction: time+ group	0.7	4	0.014	0.533
O_2Ct effects	For time	10.9	2	0.089	**<0.0001*** **
	for group	9.6	2	0.149	**0.0001*** **
	For interaction: time+ group	2.0	4	0.035	0.090
O_2Cap effects	For time	10.4	2	0.085	**<0.0001*** **
	For group	8.5	2	0.133	**0.0003*** **
	for interaction: time+ group	1.3	4	0.023	0.267
$D(A\text{-}a)O_2$ effects	For time	4.4	2	0.043	**0.013***
	For group	9.4	2	0.162	**0.0001*** **
	For interaction: time+ group	1.1	4	0.023	0.323

BEb, blood base excess/actual base excess; BEecf, extracellular fluid base excess/base excess; Ca2+, calcium; $D(A\text{-}a)O_2$, alveolar-arterial gradient; HCO_3, bicarbonate level; Na^{+}, sodium; O_2Ct, oxygen concentration; SO_2, oxygen saturation; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; SB, standard bicarbonate; O_2Cap, total blood oxygenation; η^2, Eta squared effect size; F, F-value; df, degrees of freedom; significant results ($p < 0.05$, **$p < 0.01$, and ***$p < 0.001$) are bolded.*

decompensated alkalosis with their transition to the stage of compensated alkalosis, respectively, in SG1 from 83 to 52.9%, in SG2 from 65.4 to 53.2% ($p < 0.05$), which was not observed in the control group.

Base excess is the metabolic component of ABS dysfunction. A positive value indicates metabolic alkalosis, a negative value indicates metabolic acidosis. The indicator of uncompensated metabolic alkalosis covers an increase in pH above 7.45 and an increase in the following values: BEecf, BEb, and SB. BE is defined as the amount of strong acid that must be added to each liter of fully oxidized blood to return the pH to 7.40 under normal conditions (9–12). The results presented in **Table 2** and **Supplementary Table 2** indicate that the average excess of bases in extracellular fluid, blood, and SB exceeds the reference ranges in all the groups, which also confirmed the presence of metabolic alkalosis in all the subjects from the first to the seventh day of AWS therapy. The applied methods of treatment in all the groups did not significantly affect the excess of bases for this time period, which might be quite acceptable in metabolic alkalosis, in contrast to the respiratory alkalosis. In the case of respiratory alkalosis, the use of oxygen therapy methods would effectively normalize the level of biochemical abnormalities.

The participation of the respiratory component in ABS disturbances is reflected by pO_2 and pCO_2 (**Figure 1**, **Table 1**). The change in the pCO_2 index reflects a functional pathology of the respiratory system or is the result of compensatory reactions during metabolic shifts (9). pO_2 can be defined as the oxygen pressure required to retain dissolved oxygen in arterial blood. The higher the pO_2 is, the more oxygen there will be in blood and the higher the rate of movement of oxygen from capillary blood into the tissue (9). The average group pCO_2 values in subjects with oxygen therapy were in a range below the standard values, but they did not have statistically significant differences from the standards (according to the results of a one-sample *t*-test). In CG, the average group pCO_2 was lower than the standard ones ($t = 3.4$; $p < 0.05$). Higher pH values, together with the normal pCO_2 values, can confirm the biochemical diagnosis of metabolic alkalosis. A tendency toward observing a decrease in pCO_2 in the CG group may indicate a more serious condition (10), as these subjects did not receive additional oxygen therapy methods. The average pO_2 levels in groups with oxygen therapy were in the range of the standard values, when using HBO from the first day of therapy and when using NOT from day 3 of therapy. In the CG, the mean group pO_2 values were lower than the reference ranges throughout the entire treatment period and after a week of therapy did not reach the target norm ($t = 2.9$; $p < 0.05$). The average group values of SO_2 in groups with oxygen therapy from the first day of AWS recovered to the standard values, which could not be seen in the CG group. In CG, the mean group values of SO_2 were lower than the reference ranges throughout the entire treatment period ($t = 4.1$; $p < 0.05$). To improve SO_2 values in the complex treatment of AWS, the HBO method was a priority, although the use of NOT also made it possible to restore SO_2 from the first day of its use. The number of persons (%) with pCO_2 under the normal values in CG was also greater ($p<0.05$) than in groups with the oxygen therapy. It indicated that the oxygen therapy methods were more effective than only SDT in the correction of the severity of metabolic alkalosis in AWS. In groups with oxygen therapy, compared with CG, the number of subjects with low pO_2 values decreased significantly (**Supplementary Table 1**). Therefore, the oxygen therapy methods in the complex AWS treatment, in comparison with SDT alone, reduce (from the first day of the treatment) more effectively the number of people with low saturation indices and increase the partial pressure of the oxygen. The advantages of methods of oxygen therapy over other SDT have not been established so far.

Total blood oxygen concentration (O_2Ct) and oxygen content (O_2Cap) starting from the first day of the AWS therapy were within the reference ranges in all the studied groups. The use of the HBO method in complex treatment more effectively influenced these indicators compared with the NOT method in combination with SDT and the use of SDT alone (**Table 2** and **Supplementary Table 2**). As these values in all the groups were within reference ranges, it was not subject to more detailed analyses.

The $D(A\text{-}a)O_2$ is a difference between the alveolar and arterial oxygen concentration. $D(A\text{-}a)O_2$ is useful in identifying the source of hypoxemia. This measurement helps locate the problem as either intrapulmonary or extrapulmonary (21, 22). According to **Table 2** and **Figure 1**, the use of oxygen therapy methods in the complex treatment of AWS makes it possible to reduce the $D(A\text{-}a)O_2$ levels much more effectively from the first day of therapy, when compared with the use of SDT alone ($p < 0.05$). High values of the A-a gradient are due to impaired oxygen transfer/gas exchange. They are usually associated with diseases of alveolar membrane, diffuse connective tissue diseases, or inadequacy of the ventilation-perfusion ratio. A high alveolar-arterial oxygen gradient may indicate low oxygen tension in mixed venous blood, low cardiac output, high oxygen consumption, or low hemoglobin concentration (22). Considering the normal levels of hemoglobin (**Table 1**) as well as the absence of serious problems from the cardiovascular and respiratory system in the history of all the subjects, these factors should be excluded. One of the likely factors of increased $D(A\text{-}a)O_2$ values might be a high oxygen demand in the oxidation processes (22). Therefore, the use of oxygen therapy methods in the complex treatment of AWS more effectively restores oxygen deficiency, normalizes the levels of $D(A\text{-}a)O_2$, and consequently, regulates the metabolic processes after alcohol intoxication.

In our study, the use of SDT alone or in combination with oxygen therapy methods did not have a significant effect on the levels of hemoglobin, glucose, Ca^{2+}, or Na^{+} throughout the entire period of care. Even though statistically significant differences in the hemoglobin levels were presented (**Table 1**), these values did not require further analysis because their values did not go beyond the reference ranges in almost all the subjects. It should be noted that, in all the studied groups, those subjects with Ca^{2+} levels below the reference ranges had no significant positive dynamics in its correction during AWS (**Supplementary Table 1**). Hypocalcemia can contribute to the development of neuromuscular excitability and convulsive syndrome, which, in some cases, is a kind of compensation mechanism for alkalosis since lactates are formed during tonic

muscle tension. The possible reasons for a decrease in the level of ionized calcium can include hyperosmolar states with changes in pH, pancreatitis, traumatic brain injury, and a lack of vitamin D (4, 9, 11). In our study, we also noted that levels of ionized sodium (Na^+) were within the normal range (**Table 1**) in the vast majority of subjects in all the groups, and the applied methods of treatment did not have a significant effect on it.

In the mixed ANOVA design, we showed significant interactions for time and groups in the pCO_2 value with a significant time-by-group interaction and significant interactions for time and groups in the pH and O_2Ct values with a strong tendency to significant time-by-group interaction. However, we noted statistically significant within-group changes in the *t*-test only for pH but not for pCO_2 and O_2Ct values (**Table 1**). The effect of time in the pH value had a higher effect size than for groups. A significant effect of only time for Na+ and a significant effect of only group for pO_2, SO_2, glucose, Ca^{2+}, and HCO_3^- were found. The significant effect of time and group but without significant time-by-group interaction was found for hemoglobin, BEecf, BEb, SB, O_2Cap, and $D(a\text{-}A)O_2$. Although HCO^{3-} values had significant effect only for groups, a significant decrease in HCO^{3-} value only in the CG group and a lack of decrease in oxygen intervention groups (SG1, SG2) may point on the treatment effect. Therefore, in this case, the lack of effect (as in the case of other ABS markers) may not exclude in fact the effect of oxygen therapy (NOT and HBO). In contrast, it may even indicate a positive oxygen therapy effect.

LIMITATIONS

Some limitations of this study may be due to the lack of the results of ABS markers in the healthy control group and before the treatment in the SG1, SG2, and CG groups, which could show normal levels of indicators in comparison to the treatment. Another limitation is that only male participants were recruited to the study. Other methodological limitations could also have an impact on our results. The data of our study were analyzed in two ways, namely, within-group and between-group differences. A comparison of intragroup indicators may indicate the possible influence of a method on certain indicators. Intergroup differences may point out the advantages of a particular method on the dynamics of the levels of a certain biological marker. As there were no correlations found between the CIWA-A scores and ABS markers, it might be due to the indirect effect of ethanol metabolites on ABS state and their indirect link with abstinence symptoms.

CONCLUSION

We found that subjects with moderate AWS had metabolic alkalosis phenomena. The use of oxygen therapy methods in combination with SDT in comparison to SDT alone allows for faster and more efficient correction of the markers of the metabolic alkalosis, as evidenced by the dynamics of the pH, pCO_2, and pO_2 levels; more effectively restores the saturation levels, starting from the first day of the AWS therapy, with the relative priority of the HBO method; reduces the $D(A\text{-}a)O_2$ levels much more effectively from the first day of therapy in comparison with the use of SDT alone and restores oxygen deficiency; and more effectively includes reserve capabilities of the body for the restoration of ABS mainly due to the bicarbonate (hydrocarbonate) buffer system. We can also conclude that the applied methods of treatment in all groups did not significantly affect the indicators of excess of bases, actual hydrocarbonate, and standard bicarbonate, which might be quite acceptable in metabolic alkalosis. Although the novel oxygen-related therapeutic procedures such as NOT and HBO in combination with standard drug therapy did not improve the alcohol withdrawal symptoms, it helped with the faster restoration of the ABS state. Further studies, with a control group before the oxygen therapy, should elaborate more extensively on the time and group effects of oxygenation on the AWS.

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 the Local Bioethical Committee of Belarusian State Medical University (N 8/124.15.08.2017). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DK and AK: conceptualization. DK, AK, IK, and LK: data curation and formal analysis. DK, AK, and IK: investigation and methodology. AK: project administration and supervision. DK, AK, IK, NW, and LK: writing–original draft. NW: writing–review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Development of Goal Management Training+ for Methamphetamine Use Disorder Through Collaborative Design

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Background: Methamphetamine use disorder (MUD) is associated with executive dysfunctions, which are linked with poorer treatment outcomes including earlier drop out and relapse. However, current treatments for MUD do not address executive functions. Goal Management Training (GMT) is an evidence-based cognitive remediation program for executive dysfunction, although required modifications to enhance its relevance and application within addiction treatment settings. This study aimed to (1) tailor GMT to the key cognitive deficits and typical treatment duration of MUD; (2) explore consumers' (people with MUD) engagement with the revised program; (3) implement a prototype of the program with consumers; and (4) present the manualized standard administration to clinical service providers.

Methods: We followed the Medical Research Council Complex Interventions Framework and employed an evidence- and person-based intervention development process. We used a four-phased approach and collaborated with neuropsychology experts, design researchers in healthcare, consumers with MUD, and clinical service providers. Each aim was addressed in a separate study phase; including content refinement and review with neuropsychology experts (phase 1), intervention design and collaboration with consumers (phase 2), prototype development and review with consumers (phase 3), and final program modifications and review with clinical stakeholders (phase 4).

Results: Findings from phase 1 indicated support for targeting four cognitive processes (attention, impulse control, goal setting, and decision-making). Key feedback included the need to help habitualize cognitive strategies and to guide consumers in applying these strategies in emotionally salient situations. Findings from phases 2 and 3 indicated consumer support for the program strategies and materials but highlighted the need to further enhance the personal relevance of specific content and journal activities. Findings from phase 4 provided clinicians support for the revised program but indicated an opportunity to minimize unintended effects. We present the intervention materials for the final revised program, Goal Management Training+ (GMT+), in line with TIDieR guidelines.

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Conclusions: GMT+ targets key cognitive processes and is sensitive to the clinical needs of people with MUD. Our intervention development process was important for informing the active ingredients and materials for GMT+, and indicated initial consumer and provider acceptability prior to conducting a clinical trial.

Keywords: Goal Management Training, cognitive remediation, user engagement, person-based, participatory design, collaboration, addiction, methamphetamine

INTRODUCTION

Methamphetamine is a highly addictive stimulant that presents a global public health concern (1). In 2019, ∼27 million people had used amphetamines worldwide, and there is growing concern around the rise of harmful patterns of use (2). Methamphetamine use disorder (MUD) is associated with greater risk of suffering physical and mental health conditions, including cardiovascular disease, blood-borne viruses, psychosis, depression, and suicide, as well as social disadvantage (3–5). Underlying the hallmark characteristics of MUD (i.e., loss of control over drug intake, escalation of use despite growing negative consequences) are cognitive deficits in executive functions (the higher-order cognitive skills that orchestrate goal-directed behaviors) (6, 7).

Emerging research has revealed that executive functions, such as inhibitory control, working memory and decision-making, are significantly associated with MUD treatment outcomes (8, 9). Specifically, consumers with deficits in executive functions are at greater risk of dropping out of treatment, relapsing after abstinence-oriented treatment programs, and struggling to regain quality of life (10, 11). This research, together with recent evidence showing that current treatment interventions for MUD have overall limited efficacy (4), raises the need to incorporate cognitive remediation interventions for executive dysfunction as an add-on to current treatment approaches (12, 13). Cognitive remediation interventions aim to strengthen executive functions via meta-cognitive skills and strategy learning within a therapeutic group environment (14).

In a recent meta-analysis of cognitive-boosting interventions for addiction treatment, we showed that Goal Management Training (GMT) is the most promising approach to ameliorate executive deficits in this context (15). GMT was originally developed to improve executive functions in brain injury populations (16), but its active ingredients, such as strategies to prevent disinhibited responses and manage complex tasks, are well-suited for substance use disorders (17–20). However, the original GMT presents three key limitations in the context of MUD treatment. Firstly, the length of the program is 7–9 weeks, which almost doubles the standard duration of treatment episodes for MUD (21). Second, the training activities and their delivery were not designed to address the nature and severity of cognitive deficits in substance use disorders or MUD specifically. In MUD, deficits are less pronounced than in brain injury, and there is a need for a greater emphasis on aiding long-term decision-making and inhibiting impulsive behaviors, which are key predictors of addiction treatment outcomes (8). Third, the presentation of materials (including character examples, design, and activities) may lack engagement potential for people with MUD. For example, the original program was designed to suit older adults with different demographics and may not be adequate to capture attention or personal relevance for people with MUD. In addressing these limitations, it is important to incorporate the views of people who use methamphetamine to enhance the intervention experience for the end-consumers (22) and to ultimately increase the chance of it being considered as "helpful" and acceptable.

The purpose of this study was to develop a modified version of Goal Management Training (now Goal Management Training+; GMT+) to strengthen executive function and improve clinical outcomes in individuals with MUD. Our specific aims were:

Aim 1: To develop an updated version of GMT tailored to the cognitive deficits of people with MUD and the duration of typical treatment episodes for MUD/substance use disorders.

Aim 2: To gather consumers' (i.e., people with MUD) engagement with the updated GMT program.

Aim 3: To implement a consumer-acceptable prototype of the program (i.e., GMT+).

Aim 4: To manualize the intervention, showcase a standard administration among clinicians, and prepare materials for the proof-of-concept pilot trial.

MATERIALS AND METHODS

Design and General Procedures

We followed the Medical Research Council Complex Interventions Framework (23). The intervention development process was underpinned by an evidence- and person-based approach. This approach aims to ground the development of interventions in a deep understanding of the consumer perspective, with consideration to their psychosocial context (24). Importantly, the process involves a flexible approach that is guided by understanding the needs, goals, and desires of the end consumers (i.e., people with MUD) (25). This is achieved through involving consumers in the development process as experts of their own life experiences, within a participatory design framework (26). The intervention development process incorporates multidisciplinary skills and perspectives by including cognitive and clinical psychology researchers (core research team), neuropsychology researchers,

Abbreviations: MUD, Methamphetamine Use Disorder; GMT, Goal Management Training; GMT+, Goal Management Training+.

design researchers in healthcare, consumers with MUD, and clinical service providers.

We used a qualitative approach and developed the intervention in four phases. Phase 1 involved content refinement, where the existing content was assessed for relevance for MUD and reorganized in a streamlined set of modules/sessions to bring it closer to the standard duration of MUD treatment. We then conducted a focus group with experts in neuropsychology to evaluate these changes and seek further recommendations. This was considered the intervention planning phase. Phase 2 involved intervention design. We collaborated with design researchers in healthcare to reimagine the materials and visual identity for GMT$^+$, as well as to increase the experiential engagement of activities involving the core GMT skills. Next, we conducted a focus group with consumers with MUD to gain feedback on the design and engagement with the key concepts and activities. Intervention development took place over phases 3 and 4. Phase 3 involved developing a prototype of the intervention. We conducted a second focus group with people with MUD via teleconferencing software, to review the changes from the first focus group and to test sample activities from the module and daily journal. Phase 4 included the final program modifications, including feedback gained in a review session with clinicians. We present a description of the final materials, in line with TIDieR guidelines (27).

The Monash University Human Research Ethics Committee (12364) and Eastern Health Human Research Ethics Committee (LR19/023) approved the study and all participants provided informed consent. The full study, including the four phases, took place between March 2019 and March 2021.

Original GMT Program

The original GMT program includes up to nine 2-h sessions, which include Presentation slides, therapist scripts, activity materials (e.g., worksheets and a deck of playing cards) and take-home workbooks. Sessions include character examples to demonstrate real-world concepts, in-session activities to promote experiential learning, and discussion of participants' own experiences. The take-home workbook includes "assignments", such as monitoring for absentmindedness and related consequences (16).

The program developers report a seven-session version of GMT (16); however, the nine-session version of the program has been described elsewhere (28). Session 1 aims to help participants to be aware of absentminded errors in everyday life. Session 2 builds on absentminded errors and their associated consequences. Participants learn that they can avoid making slips by building their attention. Session 3 introduces the "automatic pilot", an expression of habit that can be responsible for absentminded errors. In session 4, participants are taught to say STOP out loud to interrupt the automatic pilot and reduce slips. Session 5 introduces working memory as the mind's "mental blackboard". Participants are taught to frequently check their "mental blackboard" to protect their goals from distraction. Mindfulness meditation is introduced to build awareness of feelings, behaviors, and goals. Session 6 builds on "STOP" and mindfulness and teaches participants to "state" their goals out loud. Session 7 introduces conflicting goals in the context of decision-making and encourages the use of 'to-do" lists as a decision-making strategy. Session 8 introduces task-splitting to help participants to split unwieldy goals into more manageable steps. At this point, participants start to STOP-State-and then Split their goals. Session 9 encourages participants to Check their overall goals and to interrupt ongoing behavior that can interfere with goal achievement.

Phase 1: Planning—Streamlining GMT

Participants

We recruited neuropsychology experts ($n = 4$) who were familiar with the original GMT program for a content re-development focus group. All participants were recruited from Monash University.

Materials

The core research team updated GMT modules and program contents to tap into the key cognitive deficits associated with substance use disorders, based on systematic reviews and meta-analyses (8, 15, 29).

We restructured GMT into four 90-min weekly modules, each training a specific cognitive function. Module 1 (Be Aware) trains focused attention, module 2 (Pause) trains impulse control, module 3 (Envision Goals) trains goal setting, and module 4 (Decide) trains decision-making. See **Supplementary Table 1** for a breakdown of the original (GMT) and updated (GMT$^+$) content. GMT$^+$ is designed as a 4-staged cycle (see **Figure 1**) that can be employed by consumers in any given moment. Participants can be aware of their attention and surroundings, pause and breathe, consider their goals (short-term or long-term) and make a decision.

The revised content includes a greater focus on building a longer-term mindset, hence strengthening the decision-making components of original GMT. An example of this was the incorporation of episodic future thinking (EFT) in module 4 (Decide). EFT involves imagining future events through guided instruction (30) and has shown efficacy at improving preference for larger delayed rewards over smaller immediate rewards in substance-using populations (31, 32).

We updated character narratives that were aimed to illustrate real-world concepts, to enhance the relevance for people with MUD (e.g., younger characters with relatable employment, interests, and relationship problems). We selected in-session cognitive activities from the original program that matched GMT$^+$ training principles, such as a simple routine-based task that elicits errors due to inattention (Be Aware module), and a multitasking activity that highlights goal neglect due to distractions (Envision Goals module). We increased the rule complexity of these tasks to evoke the desired errors ("slips") in people with MUD, who have milder deficits than people with brain injury. The newly developed activities in module 4 (Decide) were designed to help to participants to practice setting and staying on track with long-term goals. We also included new strategies to demonstrate learning (e.g., presenting problem scenarios and asking consumers to suggest the most appropriate GMT$^+$ strategies).

FIGURE 1 | GMT+ cycle.

Procedures

We conducted a 2-h face-to-face focus group with neuropsychology researchers and presented the updated modules and content via presentation slides. We sought feedback on the new program structure (i.e., streamlined contents and stronger focus on decision-making), whether the active GMT training ingredients were maintained and if the new elements were appropriate for the program, and whether the overall training ingredients were appropriate in the context of addiction. Facilitators (AA and AR) took written notes throughout the session to capture verbal feedback. After the focus group, the core research team (AVG, AA, AR) met to review the data that were collected.

Phase 2: Intervention Design—Enhancing Engagement

Participants

We recruited consumers with MUD (n = 4; two women) to attend a face-to-face intervention design focus group. Participants were recruited from Turning Point, a public addiction treatment center based in Melbourne, or from eligible people who had previously participated in research with our group. Participants were compensated with a $20 grocery gift card. Eligibility criteria included a current or past diagnosis of MUD, aged 18 or over, and the absence of intellectual disability or severe neurological conditions. Seven participants consented to take part in the focus group, although three did not attend on the day.

Materials

We collaborated with design researchers in healthcare to reimagine the intervention materials and promote consumer engagement with the program. Design priorities were grouped into five categories, including material re-design, program delivery, enhancing program relevance, assessing acceptability of program delivery, and encouraging skills practice. We developed a range of fresh color palettes and fonts for the slide decks, new character designs, updated in-session cognitive task materials to encourage active engagement (e.g., sound buzzers, vintage cartoon cards), and a selection of written journal activities to gauge consumer preferences on reflective skills practice. We designed a GMT+ bracelet to serve as a visual reminder of the 4-staged cycle displayed in **Figure 1**, with the goal of encouraging participants to regularly practice GMT+ strategies to promote skill habituation.

Procedures

We conducted a 2-h focus group with consumers at Turning Point meeting rooms, employing think-aloud techniques. The format was a structured session with presentation slide content, guided questions, and ratings stickers to gauge preferences for select concepts. Focus group participants were asked to share ideas, interact with tasks and materials, and provide verbal feedback. The facilitators assessed participants' understanding by summarizing key points and checking for accuracy. Facilitators took written notes throughout the session to capture verbal and non-verbal feedback.

We sought feedback on material redesign (e.g., color palettes, fonts, logo, illustrations), ways to enhance program relevance (discussing personal goals and previous treatment experiences), delivery format (how comfortable participants were in contributing to the group), and enhanced skills practice materials (presenting new activities, assessing difficulty level and whether they produced desired errors). The core research team met after the focus group to review the data and implement the suggested changes for subsequent phases.

Phase 3: Intervention Development—Prototype

Participants

Consumers with MUD (n = 5; two women) were recruited by contacting participants from the previous consumer focus group and through Turning Point for an online focus group. Three participants from focus group 2 (75%) returned for the follow-up session. Two additional participants were recruited "*de novo*", to enable novel perspectives and prevent confirmation biases. Participants were compensated with a $25 grocery gift card for attending the focus group and an additional $15 grocery gift card for returning written materials. Eligibility criteria was the same as Phase 2. Participants required access to the Internet and a device to access the video conferencing software (e.g., smart phone, tablet, laptop). Six participants consented to take part in the focus group. On the day of the focus group, one participant did not attend.

FIGURE 2 | GMT+ journal.

Materials

We collaborated with design researchers in healthcare and developed a prototype of GMT+ to present in the intervention development focus group. The prototype included sample presentation slides, a new GMT+ ambassador character to demonstrate real-world progress throughout the program, and in-session activities relating to module 1 (Be Aware). We developed a printed journal with seven daily activities to encourage consumers to practice skills relating to module 1 (see **Figure 2**). This journal included both skills reflection activities (how participants used GMT+ skills in everyday life) and creative activities where they could practice GMT+ skills during the task (e.g., mindful drawing to regulate breathing).

Procedures

The focus group duration was 2 h and was conducted online, using videoconferencing software. The structured session included presentation slide content, guided questions, and ratings polls to gauge preferences. The prototype of module 1 was embedded in the session. We tested acceptability of the program and materials, the delivery format (including feasibility of an online delivery format), engagement with concepts and activities, engagement with the between-session journal, and the appropriateness of language. Qualitative aspects included observation of consumer engagement and their interaction style, and reviewing content themes that arose from think aloud techniques. Quantitative aspects included Likert scales to indicate acceptability of the journal content. The session was audio recorded and facilitators took written notes to capture non-verbal feedback.

Following the focus group session, we mailed out packs to attendees with the sample GMT+ journal and a pre-paid return envelope. Participants were asked to complete the journal daily, which was designed to take ∼1 h in total. A summary of the key training concepts was included in this journal. Participants were asked to time themselves completing each activity, to rate their engagement (Likert scales), and to provide written feedback. After completing the journal, participants were asked to mail it back to the researchers. Two participants returned the completed journal including their feedback.

Phase 4: Intervention Development—Clinical Acceptability

Participants

Clinicians ($n = 2$) were recruited from Turning Point and The Turner Clinics, Monash University for an online program review and feedback session. We invited clinical directors of these treatment services, due to their high level of knowledge around the needs of people with MUD and the implementation of new interventions. Neither treatment service was involved in the future pilot trial.

We also engaged clinicians ($n = 9$) from three treatment services (including metropolitan and regional locations) that had agreed to take part in the future trial to refine aspects of the final intervention delivery."

Materials

Clinical psychology researchers and design researchers in healthcare collaborated to develop the complete package of program materials, including presentation slides and presenter scripts, in-session activities, and journal activities for the four modules. We developed journal activities that appeared "enjoyable" to complete, whilst training the relevant cognitive skills. The journal activities for each week targeted building attention and meta-cognition (week 1: Be Aware), learning to pause and gain control over impulsivity (week 2: Pause), improving focus on current and short-term goals (week 3: Envision Goals), and improving future-focused reflection and long-term decision-making skills (week 4: Decide).

Procedures

We conducted a 2-h online videoconference review session with clinical treatment providers to assess reactions to the program and to further optimize acceptability and feasibility. We presented the full program including: the in-session presentation slide material and activities, and the between-session journal activities for each of the four modules. Facilitators paused for discussions during the presentation to collect ongoing feedback from clinicians. The session was audio and video recorded. Following the review session, the core research team met to discuss the clinical feedback and to incorporate the final changes to the program materials.

We then conducted meetings with clinicians from treatment centers involved in the trial to present the final program and seek feedback on intervention delivery. Following these meetings, the core research team met to discuss the feedback and to incorporate minor changes to the presenter scripts and facilitator roles during the group sessions.

RESULTS

Phase 1: Planning—Streamlining GMT

Focus Group 1: Neuropsychology Researchers

Neuropsychology experts were positive about the revised 4-session program structure and design, including GMT+ characters, who faced similar challenges to those typically encountered during MUD recovery. The experts further helped to select key learning activities (e.g., promote participant involvement in helping GMT+ characters to solve a problem) and approaches to delivering the content (e.g., including a mixture of theory, discussions, and practical activities). Key feedback from the session (see **Supplementary Table 2**) highlighted the importance of helping participants to habitualize the training concepts and to guide participants around how specific strategies (e.g., Pause) could be used in "hot" (i.e., in high level of emotionality) contexts. We responded to this feedback by prioritizing the between-session journal engagement as a tool for skill habituation and agreed on the need to develop a visual reminder to employ strategies in everyday situations.

Phase 2: Intervention Design—Enhancing Engagement

Focus Group 2: Consumers With MUD (Face to Face Session)

Participants with MUD endorsed the novel four-staged cycle of Be Aware-Pause-Envision Goals-Decide and considered GMT+ to be a valuable type of intervention that is currently missing from addiction treatment services. The results indicated initial acceptability of the journal activities, the GMT+ bracelet (see **Figure 3**), and the group-based format that included discussions with and interaction between group members and facilitators. Interaction with the revised cognitive activities (see **Figure 4** for an example) indicated that they appropriately elicited the desired errors to demonstrate executive dysfunction (e.g., missing specific details on the cartoon sorting cards). Participants thought the activities were aligned with the desired purpose and were enjoyable, with a minimum average enjoyment rating of 7/10 for each one.

Qualitative themes and program changes are summarized in **Supplementary Table 3**. Key feedback included examples of relevant personal goals and the need for simplified journal activities. We used this information to facilitate relevant goal-related discussions and developed journal activities that permitted consumers to focus on working toward multiple goal categories throughout the program (e.g., short term and long term, or across different areas of life). We also prioritized the development of single-focused creative activities that appeared relevant.

FIGURE 3 | GMT+ mindfulness bracelet.

FIGURE 4 | Interactive hand buzzers replaced a "hand-clapping" task to enhance engagement.

Phase 3: Intervention Development—Prototype

Focus Group 3: Consumers With MUD (Teleconferencing Session)

Participants with MUD who had attended focus group 2 were positive about how we had incorporated their previous feedback and expressed enthusiasm for the redesigned materials. Sharing how participants' feedback was implemented is important for building trust in and establishing commitment to the participatory design approach (26). Feedback from focus group 3 (see **Supplementary Table 4**) indicated overall acceptability of

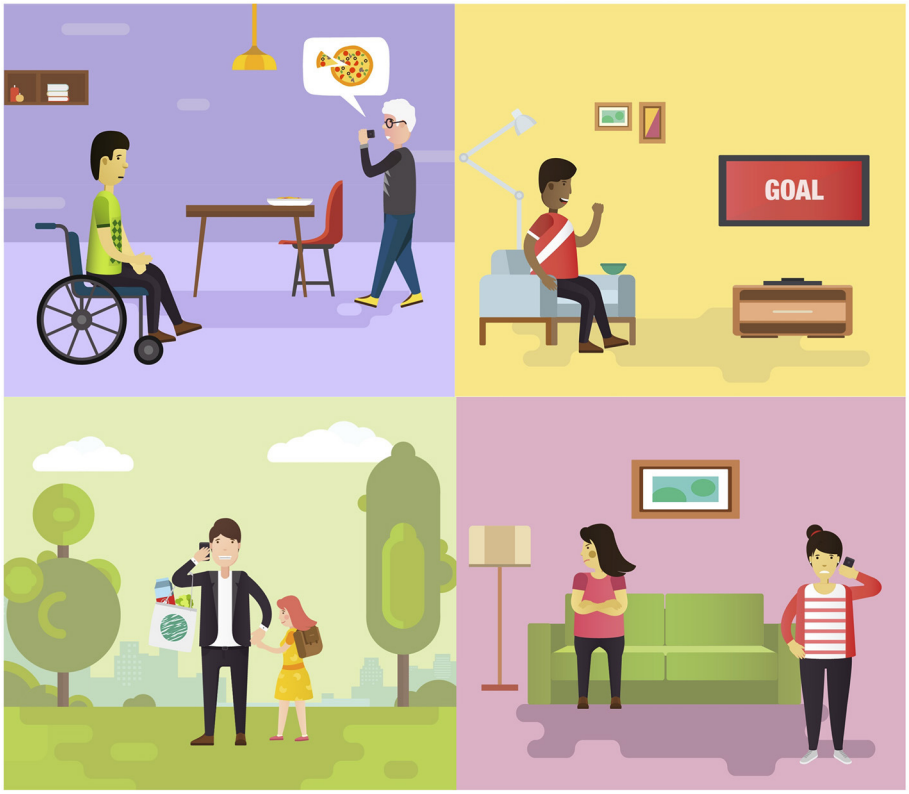

FIGURE 5 | Examples of diverse GMT+ characters.

the language used, the interactive group intervention format, and the content that was tailored to the needs of people with MUD. However, a key theme that emerged from the think aloud strategy was the need to further enhance the relevance of the program to people who are undergoing treatment for MUD. This included a greater focus on group discussions and characters with more relevant problems for this population. We responded to this feedback by addressing substance use more frequently in planned group discussions, developing a range of GMT+ characters with different demographics, attributes, and goals (see **Figure 5**), and inviting consumers to select their preferred GMT+ ambassador character to relate to in-session.

Participants indicated acceptability of the journal and affirmed that they would complete it if enrolled in the GMT+ program. Quantitative feedback indicated that the activities were enjoyable (mean rating 7.2/10), helped participants to be more aware of their attention (mean rating 6.9/10), and most activities helped them to focus on their personal goals (mean rating 6.5/10). Both participants indicated that they felt confident completing the journal activities based on the in-session strategies, discussions, and instructions provided. Finally, participants felt that the types of activities and the language used were appropriate. Participants did not complete the journal daily and one participant stated that they would be more likely to complete it regularly in an inpatient treatment setting. Completion rates and feedback highlighted the importance of reviewing journal activities at the beginning and end of each session to enhance motivation and to discuss individual experiences.

We also received important feedback on ways to improve the journal. Qualitative responses indicated that although the updated activities were creative and engaging (e.g., drawing a repetitive pattern to invoke autopilot), they required greater explanation about the relevance to GMT+ skills and everyday life. Participants enjoyed reflecting on their journal work and often provided written content beyond the provided space, suggesting a need for more reflection space on relevant pages. We addressed this feedback by providing a debrief page after each activity that explained its relevance and allowed consumers to reflect on how it may relate to their own life (see **Figure 6**). We increased the reflection text entry space across all activities.

Phase 4: Intervention Development—Clinical Acceptability

Review Session With Clinicians

Clinical treatment providers in the final review session were positive about the need for this type of intervention within addiction treatment services and considered the intervention feasible to implement. Specifically, one clinician commented favorably about how theory has been interwoven into practice "to make the whole package usable for the end-consumer." The activities were also considered "fresh" and engaging, and

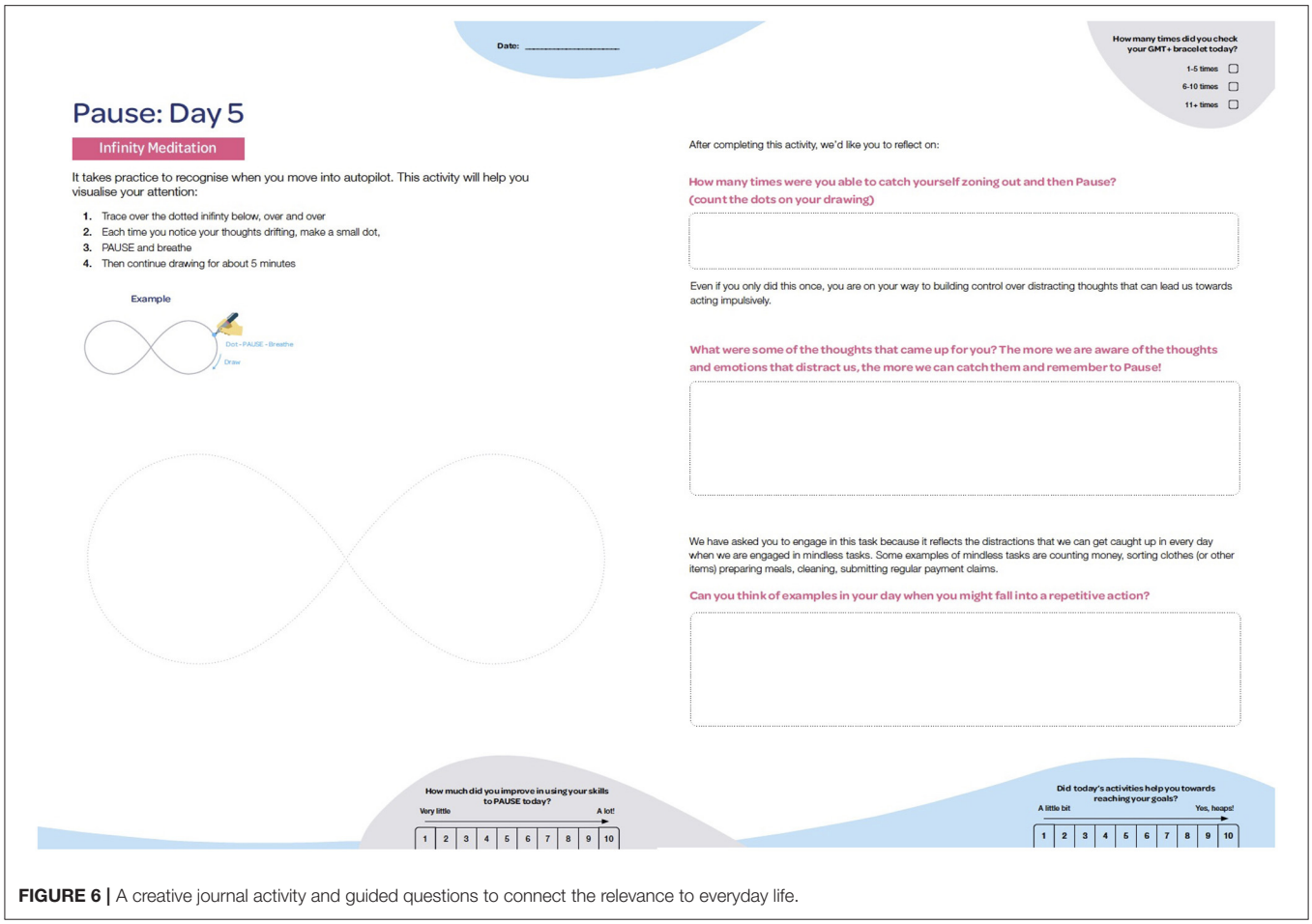

FIGURE 6 | A creative journal activity and guided questions to connect the relevance to everyday life.

appropriate for addiction treatment as the content of the stimuli is far-removed from drug-related stimuli (e.g., replacing playing cards with cartoon and travel post cards). Session feedback is outlined in **Supplementary Table 5**.

Key feedback included the need to normalize errors and slips to consumers who may be particularly sensitive to making mistakes and develop related feelings of hopelessness. We addressed this feedback by highlighting how these errors are experienced by all people and provided relatable examples of mistakes by facilitators. Clinicians also highlighted that one activity which promoted multi-tasking (even if tasks were not completed) may foster complacency with unachieved goals and reinforce procrastination. We included a debrief script to reinforce the objective of making progress toward multiple goals at the same time (to avoid neglecting one goal in favor of another).

Clinicians from the three participating treatment centers were positive about the final program materials and content, how we had addressed prior clinician feedback, and the feasibility of implementing the 4-week program within their treatment service. Key feedback included the benefit of discussing addictive behavior more broadly during group discussions, due to the high prevalence of comorbid substance use disorders, and to assess participant comprehension regularly due to low literacy levels in some clients. We modified the presenter scripts and group discussion points to enable a discussion of different examples of habitual behavior during active addiction. This included examples relating to methamphetamine use and other substance or behavioral addictions. We also divided roles of the facilitators during written tasks and when introducing journal activities, to allow one facilitator to present the content and a second facilitator to provide individual support to group members.

Key Intervention Modifications

We have made a number of changes to GMT$^+$ throughout the planning, intervention design and development phases. Some of the major changes included: (1) developing more relevant and meaningful program characters and narratives to help demonstrate everyday problems where GMT$^+$ may help; (2) adapting the language to more appropriately connect the concepts to everyday life for people with MUD; (3) developing more engaging and cognitively appropriate in-session activities; (4) developing a completely new between-session journal to increase the "hands-on" enjoyment of regular skills practice; and (5) including new strategies to develop a future focused mindset to help with decision making. We describe the final GMT$^+$

intervention, guided by Items 3–10 from the TIDieR checklist (see **Table 1**).

Goal Management Training+

The final version of Goal Management Training+ (GMT+) is a manualized therapist-facilitated targeted cognitive remediation group program. We developed a final kit comprising a range of materials to administer GMT+. The in-session materials include presentation slide content with manualized presenter scripts for each of the four modules, guided discussions, audio recordings of meditation scripts, and activity materials (e.g., sound buzzers, sorting cards). The between-session material includes a printed spiral-bound journal to distribute to each participant, consisting of daily activities that relate to the weekly module (i.e., Be Aware, Pause, Envision Goals, Decide) for them to complete. Participants record their responses in the journal. Session 1 (Be Aware) demonstrates how errors ("slips") can occur during moments of inattention. Participants learn the difference between "zoning out" (daydreaming or not paying attention) and "autopilot" (acting in a state of habit) and are taught to use mindfulness strategies to bring their attention back to the present when they begin to zone out. They make a GMT+ bracelet to serve as a visual reminder to employ these skills. Session 2 (Pause) teaches participants to regularly "breathe and Pause" to prevent zoning out or acting on autopilot. Participants consider the benefits of using Pause in emotional contexts to avoid negative consequences of habit-driven behavior. Session 3 (Envision Goals) introduces the "mental notepad" (a concept to represent working memory), where fragile goals are stored. Participants are taught to state and visualize their main goals to protect them from distractions. Session 4 (Decide) introduces short-term and long-term decision-making, and common barriers to implementing decisions. Participants are taught to set achievable goals, to break goals into manageable steps and to vividly pre-experience the achievement of a salient future goal to aid motivation. **Table 1** outlines a breakdown of content, in-session activities, and between-session journal activities. GMT+ is a variation of copyrighted material. Provided that the original developers agree, materials can be requested for research purposes by contacting the corresponding author.

GMT+ facilitators should undertake training and be familiar with the content and manuals prior to administering the intervention. GMT+ is designed as an in-person (face-to-face) intervention that should be delivered on-site by two facilitators at an inpatient addiction treatment facility. The facilitators will need access to a projector screen and computer (to run the presentation slide content), tables (as participants work with physical materials) and a quiet room. There are four weekly sessions that run for 90 min and should be delivered in groups of 4–8 program participants. A 15-min break is provided half-way through the session to minimize fatigue. The journal contains detailed instructions for daily completion and does not require any input or participant monitoring from staff at the treatment facility. Between-session journal completion is discussed as a group at the beginning of sessions 2–4 and the facilitator will assess for daily completion.

DISCUSSION

This study aimed to update GMT (a cognitive remediation program for brain injury) to tailor it to the key cognitive deficits and treatment context of MUD, and to maximize users' engagement with its contents and delivery. We utilized an evidence- and person-based approach, collaborating with neuropsychology experts, designers in healthcare, people with MUD and clinical providers to develop the novel GMT+ program. Results from our four-phased approach provide initial evidence that GMT+ may be engaging for consumers and may be feasibly applied in addiction treatment settings. These findings illustrate the benefits of the evidence- and person-based approach and provide greater confidence to move into the evaluation phase with a protocol that has considered potential risks, for example, barriers to implementation, or a lack of consumer engagement.

The initial focus on four cognitive processes (i.e., attention, impulse control, goal setting, decision-making) was endorsed by neuropsychology experts and consumers. We selected these four components based on consistent evidence revealing impairments in these specific executive functions, as well as their relationship with key addiction treatment outcomes (8, 9, 11, 33). One of the primary goals of addiction treatment is to help individuals to develop self-control strategies to manage cravings and emotionally salient situations, skills that inherently rely on these prioritized cognitive processes.

The updated GMT+ program trains these components through strategy learning, fostering skill practice in everyday situations, and reinforcing a simplified reflection-action cycle to employ in any given moment [Be Aware (of inattention)- Pause (to prevent acting on autopilot)- Envision Goals (to prevent goal distractions)- Decide (to consider longer-term outcomes)]. Consumers build on these skills as they progress through the program, providing an opportunity for skill acquisition and mastery through self-initiated practice and active reflection regarding action selection and analysis of potential related consequences. Unlike some existing interventions that train specific cognitive processes through repetitive task practice, e.g., computerized working memory or inhibitory control training (34, 35), GMT+ teaches consumers to group multiple skills together and apply them in ecologically relevant situations (for example, noticing drug-cravings, taking a deep breath, and bringing attention back toward long-term goals).

Neuropsychology experts highlighted the need to help participants to habitualize strategies to promote their effectiveness in critical real-world situations. We addressed this suggestion by including a GMT+ mindfulness bracelet to serve as a specific visual cue to promote a stimulus-response association (36), for example, noticing the bracelet and applying "Pause". As this bracelet is always accessible to consumers, it may enhance the chance of successful habit formation while participants are in the early phase of skill acquisition (37). We also incorporated activities in the take-home journal to encourage consistency of practice and skill mastery (37, 38). For example, a checkbox to note how many times consumers used their bracelet each day, activities to reflect on how different GMT+ skills were employed that day, and creative activities that

TABLE 1 | Description of in-session content, in-session activities and between-session journal activities for the four GMT+ modules.

Module	In-session content	In-session activities	Journal activities
Be aware	Introduction to GMT+. Participants select their preferred GMT+ ambassador character (3 choices). This character demonstrates errors and progress throughout the GMT+ program. Defining simple goals and complex goals. Defining short-term goals and long-term goals. GMT+ ambassador character: Introduce a situation where the character was not focussed on their overall goal and became distracted and made "slips". The group discusses potential consequences and similar personal experiences Introduce the concepts of "zoning out" and "autopilot"; how they differ; and how they can lead to slips. Practicing present mindedness. Five-minute breath meditation script. Discuss how present mindedness can prevent "zoning out" and "autopilot" Introduce this week's journal activities.	Bouncer buzzer: participants are instructed that they are a bouncer at a venue and have been tasked to press their buzzer to let every name into the venue, except "David". Names appear in succession. Task is designed to foster mistakes by pressing the buzzer for David. Mindfulness bracelet: participants weave their own GMT+ bracelet; mindfully being aware of this creative experience. They then wear the bracelet on their wrist as a reminder to practice GMT+ skills. Activity is designed as a visual leave behind reminder to encourage habitual use of GMT+ skills.	Signature on repeat: Participants detect when they slip into autopilot when writing their signature repetitively. They then draw their attention to deliberate changes to their signature. Zentangles: Participants draw repetitive shapes and notice when they have zoned out by detecting changes in the shape. Goal bubbles: Participants write their small and big goals in different areas of life (e.g., family, career, hobbies). Cone of awareness: Participants practice present-moment awareness and reflect on their thoughts while sitting silently for 5 min. Time to Reflect: Participants reflect on how they used different GMT+ skills that day (complete 3 × per week).
Pause	Recap previous material and discuss journal completion. Demonstrate how "slips" occur in a card sorting activity. Introduce "Pause" as a way to interrupt "zoning out" or being in "autopilot" mode. Discuss making a habit out of Pause. Participants are prompted to use their GMT+ bracelet as a reminder to Pause. Linking the breath to Pause (Pause then breathe), practicing breath meditation. Discuss how Pause could have helped the GMT+ ambassador character in week 1. Link Pause to emotionally aroused moments ("hot contexts"). Discuss character example of acting without thinking when emotionally aroused. Group discusses potential consequences and shares similar personal experiences. Discuss examples of everyday situations when it is important to Pause and breathe (e.g., when stressed or tired). Introduce this week's journal activities.	Cartoon card sorting: participants quickly divide cards into two piles according to a specific rule. This task demonstrates how slips can happen in routine tasks. The task is then repeated with a reminder to Pause to help reduce the number of slips made. Bouncer Buzzer: repeat bouncer task from Be Aware module, with occasional reminders to Pause to reduce the number of slips made. Facilitators highlight client progress from last week.	Draw your breath: Participants draw a continuous line to reflect the in-breath (draw upwards) and out-breath (draw downwards). This continues across the page, with the goal that the line becomes smoother, reflecting slower and more relaxed breaths. Body maps: Participants draw where they feel stress, anxiety, anger, or excitement in the body. These are cues of the autopilot taking over. Infinity meditation: Participants draw a repetitive shape and Pause, drawing a small mark, each time they have zoned out or entered autopilot. Dot-to-Dot (picture of a tiger): Participants are instructed to breathe and Pause after every five dots to maintain focus and avoid making an error in the drawing. Time to Reflect: Participants reflect on how they used different GMT+ skills that day (complete 3x per week).

(Continued)

TABLE 1 | Continued

Module	In-session content	In-session activities	Journal activities
Envision Goals	Recap previous material and discuss journal completion. Introduce "mental notes", which are the goals in our working memory. These mental notes (goals) are fragile messages in our mind that can be overwritten by distractions. Participants learn to check their "mental notepad" to protect their main goal. Character examples of how distractions can cause us to neglect our goal if we're not actively focusing on it. Highlights practical (late for work) and emotional (strained relationships) consequences. Participants are taught how to become aware of distractions and to refocus on the main goal in their mental notepads. Envisioning short-term goals: Stating goals out loud and visualizing goals as words or pictures in the "mental notepad". Participants visualize achieving short-term goals ahead of time. Introduce this week's journal activities.	Vintage travel card sorting: Participants sort the cards into two piles according to a specific rule. Distractor words are called out during the task and participants must note when the same word is called twice. The task is then repeated with a reminder to Pause to help reduce the number of slips made. Multitasking activity. A series of activities are introduced and participants are given a short time limit to complete the task. The main goal is to attempt each task and bonus points are provided if this goal is achieved. The task is designed to distract from the main goal as each task is detailed and time-consuming to complete. The multitasking activity is then repeated with the main goal explicitly highlighted as the key focus. Participants state the goal out loud before starting and occasionally throughout the task. Improved performance on the task is highlighted to the group.	Goal distractors: Participants consider their biggest goal distractors and ways to overcome these distractions (using GMT$^+$ skills). Short-term goal: Participants write one goal for the next day and then visualize achieving it. They later reflect on whether this goal was achieved. Word search: Participants complete a word search and focus only on the goal words, ignoring various distractor words. Returning to goals: Participants practice returning to a specific goal multiple times throughout a task. This task is designed to encourage participants to frequently return to other goals during the day. Blackout poetry: Participants are tasked to black out all words in a short passage except five words that will form a short poem. Task is designed to train focussed attention and working memory. Time to Reflect: Participants reflect on how they used different GMT$^+$ skills that day (complete 3 × per week).
Decide	Recap previous material and discuss journal completion. Introduce decision-making and long-term goals. Long-term goals can be interrupted when (1) there is uncertainty around what to do, or (2) when the decision is clear, but motivation is low. Using SMART goals to plan for long-term goals. Task-splitting long-term goals into manageable steps. Managing multiple long-term goals. Participants are prompted to consider their goal priorities and to create a hierarchy of most important to least important goals. Introduce Episodic Future Thinking (EFT) to visualize achieving long-term goals in order to aid short-term motivation. Recap of entire program: Participants are presented with different scenarios where characters have implemented some GMT$^+$ strategies but have forgotten at least one important component. Participants discuss which GMT$^+$ strategies could help the character. GMT$^+$ ambassador character: Participants return to the GMT$^+$ character they selected and offer suggestions to prevent the initial slips this character faced in session 1. Summarize key content of GMT$^+$ and introduce this week's journal activities.	SMART goals: Participants create SMART goals for a goal that they would like to achieve in the next 6 months. The goal should be Specific, Measurable, Achievable, Relevant, and Time specific. Activity is designed to help participants with long-term goals when they are unsure about where to start. Daily planner: Participants create a daily planner to manage multiple long-term goals. Designed to avoid goal-neglect when there are multiple important long-term goals. Episodic Future Thinking exercise. Participants envision a future experience of achieving a goal in 3 months. Guided future meditation exercise to evoke rich detail about the experience of achieving a future goal.	SMART goals: Participants create a SMART goal for a goal that they would like to achieve in 1 month. Goal distractors: Participants consider distractors that may interfere with achieving long-term goals when they feel triggered toward using substances. They reflect on different GMT$^+$ skills that can help to manage distractors. Relationship goals: Participants creatively reflect on a future relationship goal by drawing a picture. Visualize: Episodic Future Thinking activity to reflect on detailed aspects of achieving a future goal. Designed to help participants to pre-experience this feeling of goal achievement. Time to Reflect: Participants reflect on how they used different GMT$^+$ skills that day (complete 3 × per week).

were superficially enjoyable (e.g., dot-to-dot, mindful drawing) but required the use of GMT+ skills to complete.

Consumers provided input on their personal goals during recovery and emphasized the need to develop relatable characters and scenarios. We used this feedback to create a range of character profiles and situations where a character may have benefited from applying GMT+ strategies. We provided consumers with the opportunity to personalize their group treatment by selecting their preferred GMT+ ambassador character to enhance meaning and motivation to engage in group discussions (39). Consumers indicated a preference for simple and creative journal activities with a clear purpose. We responded to this feedback by creating intuitive and enjoyable activities requiring minimal instructions and including clear links to everyday challenges for consumers to reflect on. We reason that these activities will be well-suited to promote strategy habituation due to anticipated adherence to regular journal completion (skills practice). Amending the language and visual representation of key strategies was an important aspect of our development process. For example, consumers preferenced the word "Pause" over the original "Stop," which was considered punitive, for labeling Module 2.

The final showcase to clinicians identified important unintended effects, for example, GMT+ uses multitasking (even if all activities are not completed) and task errors as ways to illustrate challenges for executive function; however, these aspects may trigger procrastination and perceived hopelessness. We addressed this feedback by enhancing the context around these activities (i.e., explaining the aim as "making progress toward goals"). Facilitators are also prompted to share personal accounts of everyday "slips" to group members and to normalize mistakes on the tasks as part of the learning process, with the goal of reducing feelings of shame or a tendency to overidentify with making errors. An additional benefit might also be to promote self-compassion during a fragile treatment period where self-criticism may be more likely to lead to earlier program drop-outs and re-engagement in addictive behaviors (40, 41).

Strengths and Limitations

There were several strengths to our design process. We employed four diverse groups in the development process, including neuropsychology experts, design researchers in healthcare, consumers with MUD, and clinical service providers. We conducted both face-to-face and online focus groups with consumers, providing an indication of positive engagement with future online administration. Our person-based, participatory design perspective valued and incorporated the needs and experiences of the end-consumer at each intervention development phase. In addition, our intervention development model has synergies with Stage 0 (the evidence-based research guiding our content changes) and Stage I (intervention refinement, involving the target population and clinical providers, and preparation for pilot testing) of the established NIH Stage Model for Behavioral Intervention Development (42). This provides confidence that we have followed the recommended initial steps in intervention development and are now ready to move into pilot testing.

There were some limitations to our work. There were only four participants in focus group 2 and five participants in focus group 3, potentially limiting the perspectives provided from consumers with MUD. We included participants with both current and past methamphetamine use. It is possible that the perspectives of those who no longer used methamphetamine are not representative of a population currently undergoing treatment. However, this concern is balanced by the benefit of receiving perspectives from people who understand the treatment process and have maintained abstinence. There were also only two clinicians in our intervention review session, which limits clinical perspectives on the finished program. However, clinicians from the addiction treatment services involved in the pilot trial agreed with the feedback and subsequent changes and endorsed the final intervention materials. Further, we only tested a prototype of module 1 (Be Aware) due to time constraints. Although we tested key concepts from other modules (e.g., Pause, the mental notepad, EFT), the presentation slide materials and journal activities for modules 2, 3, and 4 were not delivered in their final form to the end-consumer. However, clinical service providers were positive about the final materials for all four modules.

Future Research

The main components of GMT+ are relevant not only to MUD but also other substance use and addictive disorders. This research may inform the development of modified interventions for different addictions, incorporating similar evidence- and person-based design principles. This paper also highlights the importance of collaborating with end-consumers prior to administering existing evidence-based interventions in different consumer populations. We employed several changes to design, training concepts, relevance of characters, and how the strategies were practiced between sessions to aid habituation.

There is also a potential to expand this intervention to treat other mental health needs where there are executive dysfunctions and difficulties with goal-related decisions, for example, binge eating disorder, ADHD, or schizophrenia (14, 43, 44). This program may also be appropriate to apply to other populations where shorter administration times and less content repetition are indicated (e.g., OCD) (28). To adapt the intervention for these groups, content changes would need to apply, such as tailoring character examples to these groups and raising discussions about how GMT+ skills could be applied for everyday difficulties. Consultation with specific service providers and relevant consumer groups could assist with these changes.

We now plan to commence a proof-of-concept pilot trial to determine the feasibility and acceptability of GMT+ as an adjunct inpatient addiction treatment for MUD. This trial will indicate the benefit of GMT+, compared to psychoeducation-control, at improving executive functions and clinical outcomes including treatment retention, substance use, craving, and quality of life (specific details are included in the trial registry; Trial ID: ACTRN12621000172808).

CONCLUSIONS

We have presented the systematic development of GMT+, an updated version of GMT that is tailored to key cognitive deficits and treatment requirements for MUD. GMT+ is a 4-week group program with a between-session journal to foster everyday skill practice. It includes clear and practical strategies to employ in everyday situations and is designed to improve attention, impulse control, goal setting and decision-making in MUD. By employing an evidence- and person-based approach, we have demonstrated how potential barriers to engagement and uptake by consumers can be addressed through modifications to the intervention content, materials, and delivery format. As such, we are confident that we have developed an intervention with initial acceptability for the treatment of MUD. However, further research is now required to further assess acceptability and feasibility, and the efficacy of GMT+ in a pilot trial.

DATA AVAILABILITY STATEMENT

The raw de-identified 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 Monash University Human Research Ethics Committee and Eastern Health Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AA: conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, and writing—review and editing. AR: conceptualization, data curation, project administration, investigation, and writing—review and editing. EP and BK: data curation, project administration, investigation, resources, and writing—review and editing. DF: project administration, resources, and writing—review and editing. DL: funding acquisition, supervision, and writing—review and editing. AV-G: conceptualization, data curation, investigation, methodology, funding acquisition, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Current Trends and Perspectives in the Immune Therapy for Substance Use Disorders

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Substance use disorders (SUDs) are an extremely challenging category of disorders because of the high rate of relapse, lower life expectancy, important rate of psychiatric and somatic co-morbidity, lack of patients' insight during most of the disease duration, healthcare costs, etc. One of the reasons to consider these disorders very difficult for physicians and the healthcare system is the lack of adequate pharmacological agents with long-term proven efficacy. So far, there are no Food and Drug Administration (FDA) or European Medicines Agency (EMA)-approved treatments for most of the SUDs, except for alcohol use disorder, nicotine use disorder, and opioid use disorder. Immunotherapy has been considered a possible solution to SUDs because it may selectively target a certain drug of abuse, it may have a long-lasting effect (several weeks or months), and it ensures an adequate therapeutic adherence. The objective of this paper was to establish the current stage of research in the field of SUDs vaccines, based on a brief literature review. Vaccines for cocaine and nicotine dependence have reached phase III trials, while other researchers are focusing on passive immunization therapy for methamphetamine use disorder. New generations of vaccines are currently explored, and they are based on superior technologies compared to the first generation of immune therapy (e.g., viral transfer genes, more immunogenic adjuvants, or higher specificity haptens). Therefore, finding immune therapies for substance use disorders SUDs remains a matter of interest, and this approach may be useful for the management of an extremely dangerous and versatile psychiatric pathology.

Keywords: substance use disorders, vaccines, immune therapy, cocaine use disorder, nicotine use disorder

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INTRODUCTION

Substance use disorders (SUDs) represent a complex and polymorphic pathology with severe psychological, social, and biological negative consequences (1). SUDs are responsible for significant rates of worldwide morbidity, mortality, quality of life impairments, financial and social burden, thus representing a major challenge for patients, their physicians, and caregivers, but also for the society and health care systems (2, 3). Despite SUDs' importance, there are currently only a few U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA)-approved medications, and for only a limited number of addictions, i.e., alcohol, nicotine, and opioid dependence (2, 3).

In the context of the COVID-19 pandemic, the problem of SUDs received increased attention, since recreational drug use may be perceived as a harmless way to cope with lockdown or isolation

stress, and not as a gateway to addiction (4). Psychosocial stressors are well-known risk factors for SUDs, therefore search for new methods to cope with the challenge of substance abuse received a new impulse in the pandemic context (4, 5).

SUDs are frequently associated with psychiatric disorders or somatic diseases comorbidity, a phenomenon that lower life expectancy, alters patients' adherence to other, prescribed psychotropic or somatic treatments, increases healthcare costs, and decreases the probability of a complete functional recovery (6–8). Because there is a limited choice of drugs available for the treatment of SUDs, and these options are often criticized for the high rates of relapse, new strategies are acutely needed for these patients (9). The need to re-configure SUDs therapeutic management using a long-term approach, and not treatments focused only on the acute episodes of substance abuse, is supported by evidence like patients' lack of insight, high rate of treatment discontinuation, high risk of complications, and personality factors that are maintaining the addictive patterns (9–11). Therefore, a change of paradigm from orally-administered medicines to long-acting injectable treatments may be beneficial for patients, and the use of intramuscular injectable extended-release naltrexone is the first step in this direction (10, 12). Unlike oral naltrexone, the injectable formula does not imply first-pass metabolism in the liver, which allows for lower doses administration and lower peak plasma concentrations (10, 12).

Immunotherapy is another way to conceive a long-term treatment for SUDs with a focus on increased adherence and reduced risk for relapse. Another advantage of immunotherapy is targeting selective drugs of abuse, e.g., heroin, which is different from the non-selectivity of currently available, orally administered μ-opioid receptor (MOR) antagonists, for example (13). Unlike orally administered MOR antagonists, SUDs vaccines do not imply the need for prior detoxification, nor do they require daily supervision of treatment adherence.

The development of a vaccine, based on a hapten structurally similar to the target drug, which is conjugated to an immunogenic carrier protein, is considered able to elicit serum IgG antibodies and was associated with positive results in preclinical models of addiction (e.g., decreased drug self-administration, and attenuated the reward effects) (14). These antibodies are expected to sequester the target drug in order to prevent its entry into the brain, acting as an antagonist for the circulating drugs of abuse (14).

Several challenges are difficult to overcome, although significant progress has been made in this domain: lack of protection against a structurally dissimilar drug with the same pharmacodynamic properties as the drug of choice, lack of a significant effect over craving, which is responsible for relapse, and significant variability in antibody formation and their duration of life within blood circulation (15). The nature of haptens and adjuvants is very important in order to obtain a sustained and efficient response after the vaccine administration, in patients with SUDs. Despite the failure of first-generation conjugate vaccines against cocaine and nicotine in clinical trials, second-generation vaccines have shown superior results in preclinical models (14).

Regarding *the general benefits* of vaccines for SUDs, it is important to mention that this approach can offer the possibility of much closer treatment adherence monitoring (because the injectable treatment is administered only by a health care specialist, and it is not self-administered as the oral treatment), there are virtually no pharmacokinetic interactions, and these vaccines may significantly decrease the risk of overdose. *The limitations* are related to the variable titer of anti-bodies produced after vaccines administration, different selectivity and affinity of these products, and to the need to accept an injectable treatment by patients with low motivation for any type of therapy.

Combining multiple types of immune therapy, like an association of anti-drug antibodies with synthetic enzymes -that are able to stimulate abused substances metabolism- has also been investigated in preclinical models of SUDs (16). The purpose of this strategy was to explore the possible complementary action of anti-cocaine antibodies when added to cocaine hydroxylase (CoH) to decrease the drug uptake in the brain and to block the centrally-evoked locomotor stimulation (16). Synergistic actions of these types of interventions warrant further exploration in the treatment of selected SUDs (16). These methods involve viral gene transfer for a specific enzyme, e.g., CoH derived from human butyrylcholinesterase with the help of an adeno-associated viral vector, but these interventions are not yet approved for human trials (17).

OBJECTIVE

The primary objective of this review was to establish the stage of the current research in the field of SUD vaccines. The analysis of efficacy and tolerability of the investigational products targeting SUDs was based on a brief review of the clinical trials.

METHODOLOGY

The search for investigational immunization products targeting SUDs included main clinical trials repositories run by the United States National Library of Medicine and the National Institutes of Health (clinicaltrials.gov) and the European Union (EU Clinical Trial Register). All phases of clinical investigation (I to IV) were considered for this review if trials were focused on specific SUDs and enrolled adult population.

In the second stage of this review, identifiers of the first stage-collected trials were included as keywords in the main electronic databases (PubMed, MEDLINE, Cochrane, Web of Science (Core Collection), PsychINFO, Scopus, and EMBASE in order to find associated, relevant articles containing study results. All *in-extenso* papers found in this stage were reviewed, and data about clinical trials methodology and results were synthesized in **Table 1**. If no published, relevant data were found in the second stage for specific trials, only methodological aspects were mentioned in **Table 1**. Data referring to animal studies were not included in the review.

TABLE 1 | Active and passive immunization in SUDs.

Anti-nicotine immunotherapy

Nr.	CT identifier	I.P.	CT phase	Methods	POM and results
1.	NCT00996034 (18)	NicVAX (3′AmNic-rEPA)	II	Occupancy of β2-nAChR by nicotine at baseline and following the administration of NicVAX 4–400 μg, using [123I]-5-IA-85380 SPECT; *N* = 11 healthy smokers; open-label	POM: mean of the average nicotine binding at scan 1 and 2 (baseline and 3 months) Results: Nicotine binding to β2-nAChR correlated positively with nicotine injected before but not after vaccination. The daily number of cigarettes and desire for a cigarette decreased after vaccination.
2.	NCT00598325 NCT00318383 (19)	NicVAX	II	Efficacy of NicVAX 200 and 400 μg 4–5 times over 6 months vs. placebo, *N* = 301 healthy smokers, DBRCT	POM: Anti-nicotine antibody concentration between screening and week 20, and from week 19 to 26, respectively Results: Vaccine recipients with the highest serum antinicotine antibodies level (top 30% AUC) were significantly more likely to attain 8 weeks of continuous abstinence (weeks 19–26) vs. placebo
3.	NCT00369616 (20)	NIC002	II	Efficacy and tolerability of NIC002 5 i.m injections vs. placebo, *N* = 341 smokers, DBRCT	POM: Abstinence rate (self-reported and measured by CO in exhaled air), immunogenicity (IgG antibodies measured by ELISA), safety and tolerability Results: The vaccine was safe, well-tolerated, and highly immunogenic after the first injection. The abstinence rate at month 2 was significant in favor of the vaccine., but continuous abstinence between months 2 and 6 was not significantly different. At 12 months, the difference in continuous abstinence rate between I.P. and placebo favored the I.P. only in those with high antibody response.
4.	NCT01304810 (21)	NicVAX	III	*N* = 300 participants who received 6 injections of NicVAX in previous trials, phase III, DBRCT, follow-up study, observational	POM: nicotine antibody levels 24 months after injection Results: undisclosed
5.	NCT01318668, EudraCT Number: 2010-019381-90 (22)	NicVAX	I/II	Effects of NicVAX 400 μg vs. placebo over CNS activation and behavior following a nicotine challenge, using fMRI, *N* = 48 participants, smokers of ≥10 cigarettes per day, DBRCT	POM: fMRI at 18 and 20 weeks post-vaccination, and reaction time in a battery of psychomotor tests Results: No difference in brain activity to smoking cues between treatment groups; no effects of acute nicotine challenge were observed, either.
6.	NCT01102114 (23)	NicVAX	III	Efficacy, immunogenicity, and safety of NicVAX as an aid to smoking cessation, *N* = 1,000 healthy smokers, 6 doses over 6 months, DBRCT	POM: Efficacy of NicVAX in reaching abstinence (by self-report and CO confirmation) during 12 months Results: undisclosed
7.	NCT01178346 (24)	NicVAX	III	Pharmacoeconomic of NicVAX vs. placebo, *N* = 500, non-randomized	POM: Health-related QoL changes during NicVAX administration – one-year monitoring Results: undisclosed
8.	NCT01672645 (25)	NIC7-001, NIC7-003	I	Safety and tolerability of NIC7-001/003 vs. placebo, *N* = 277 healthy smokers, DBRCT	POM: Adverse events (local and systemic) Results: undisclosed
9.	NCT01478893 (26)	SEL-068	I	Safety and pharmacodynamics of SEL-068 vs. placebo, DBRCT, *N* = 82 healthy smokers	POM: Frequency and severity of adverse events during 36 weeks Results: undisclosed
10.	NCT00836199 (27)	NicVAX	III	Efficacy, immunogenicity, and safety of NicVAX vs. placebo, *N* = 1,000, 6 doses over 6 months, DBRCT	POM: One-year abstinence rate under NicVAX as an aid to smoking cessation Results: undisclosed
11.	NCT00218413 (28)	NicVAX	II	Safety and immunogenicity NicVAX 100, 200, 300, or 400 μg, *N* = 51 smokers, open-label	POM: Antinicotineantibody concentrations from baseline to day 365 Results: undisclosed
12.	NCT00995033, EudraCT Number: 2008-005894-36 (29)	NicVAX, varenicline	IIb	Efficacy and safety of NicVAX/placebo + varenicline, *N* = 558 healthy smokers	POM: Long term abstinence (1 year) Results: undisclosed
13.	NCT01280968 (30)	NIC002 (NicQBeta) + Aluminum hydroxide vs. placebo	II	Efficacy of NIC002 100 μg 4 injections over 3 months vs. placebo, *N* = 52 smokers, DBRCT	POM: Vaccine induces percent change in brain nicotine AUC/Cmax/T1/2/initial slope of brain nicotine accumulation after a single/multiple puffs Results: submitted, but yet unpublished

(Continued)

TABLE 1 | Continued

Nr.	CT identifier	I.P.	CT phase	Methods	POM and results
Anti-nicotine immunotherapy					
14.	NCT00736047, EudraCT Number: 2007-006741-40 (31)	NIC002	II	Efficacy, safety, tolerability, and immunogenicity of NIC002 vs. placebo, *N* = 200 smokers, DBRCT	POM: Smoking status, exhaled CO (12 months) Results: disclosed, but unpublished
15.	NCT00633321, EudraCT Number: 2005-000922-22 (32)	TA-NIC	II	Efficacy and safety of TA-NIC 100 or 250 μg vs. placebo, *N* = 522 smokers, DBRCT	POM: Smoking quit rate of minimum 4 weeks determined at week 26 (self-report and CO breath test data) Results: submitted, but yet unpublished
Immunotherapy for cocaine use disorder					
16.	NCT00965263 (33)	TA-CD	II	Evaluation of the relation between antibody titers and the effects of smoked cocaine on rates of intoxication, craving, and cardiovascular effects, TA-CD 82 or 360 μg administered 4 times, *N* = 10, DBRCT	POM: Cocaine intoxication during 13 weeks (effect evaluated by VAS) Results: Peak plasma antibody levels significantly predicted cocaine's effects. Patients with higher titers of antibodies had an immediate and robust reduction in ratings of VAS, while those in the inferior half showed only non-significant attenuation. Self-reported use of cocaine tended to decrease as a function of antibody titer. Higher antibody titer predicted significantly greater cocaine-induced tachycardia.
17.	NCT00969878, EudraCT Number: 2008-002183-34 (34)	TA-CD	II	Efficacy of TA-CD 82 or 360 μg administered 4 times vs. placebo, *N* = 300 patients with CUD, DBRCT	POM: Rate of at least 2 weeks cocaine abstinence during weeks 9 to 16 (cocaine-free urines) Results: Almost 3-times fewer high-level anti-cocaine IgG subjects dropped out compared to low-titers subjects. No difference between the three study groups was detected by the POM for the full 16 weeks of the trial. After week 8 more vaccinated than placebo subjects attained abstinence for ≥2 weeks, but not significant. No treatment-related SAE withdrawal was reported.
18.	NCT00142857 (35)	TA-CD	IIb	Efficacy of TA-CD 360 μg administered 5 times vs. placebo, *N* = 115 CUD patients maintained on methadone, DBRCT	POM: At least 2 weeks cocaine abstinence during weeks 9 to 16 after vaccination Results: Subjects reaching high levels of serum IgG anti-cocaine antibodies (≥43 μg/ml) had significantly more cocaine-free urine samples than those with low levels and those receiving placebo, during weeks 9 to 16. Subjects with a 50% reduction in cocaine use were significantly more in the high IgG titers group vs. low IgG levels. No SAE related to treatment was reported.
19.	NCT02455479 (36)	dAd5GNE	I	Safety and preliminary efficacy of the vaccine vs. placebo, *N* = 30 (estimated) CUD patients, DBRCT	POM: General and specific safety parameters Results: the trial is ongoing as of February 2022
Immunotherapy for methamphetamine use disorder					
20.	NCT01603147 (37)	ch-mAb7F9	I	Safety of the I.P. vs. placebo, *N* = 42 healthy volunteers, DBRCT	POM: Adverse events, vital signs, ECG, clinical laboratory testing over 21 weeks Results: undisclosed
21.	NCT05027451 (38)	IXT-m200	I	Safety, tolerability, and pharmacokinetics of a 3 g single-dose i.v.- administered I.P. vs. placebo, *N* = 9 healthy subjects, DBRCT	POM: Treatment-related AE assessed by physical examination, ECG, laboratory testing, and vital signs during 127 days Results: undisclosed
22.	NCT03336866 (39)	IXT-m200	I/II	Efficacy of I.P (6 or 20 mg/kg i.v. dose) to change methamphetamine concentrations in blood and to alter methamphetamine feels vs. placebo, *N* = 56 MUD, DBRCT	POM: Change in plasma methamphetamine AUC or Cmax after challenges following single i.v doses of I.P. (29 days) Results: submitted, not yet published

CT, clinical trial; I.P., investigational product; POM, primary outcome measures; DBRCT, double blind randomized clinical trial; β2-nAChR, β2-containing nicotinic acetylcholine receptors; SPECT, single photon emission computed tomography; CNS, central nervous system; AUC, area under curve; QoL, quality of life; i.m, intramuscular; i.v, intravenous; VAS, Visual Analog Scale; CUD, cocaine use disorder; SAE, serious adverse event; ECG, electrocardiogram; AUC, area under the curve; MUD, methamphetamine use disorder.

TABLE 2 | Synthetic presentation of clinical trials for immune therapy in SUDs.

Phase I	Phase II	Phase III	Phase IV
NUD $N = 3$	NUD = 9	NUD = 4	-
CUD = 1	CUD = 3	-	-
MUD = 3	MUD = 1	-	-

NUD, nicotine use disorder; CUD, cocaine use disorder; MUD, methamphetamine use disorder.

RESULTS

A number of 22 phase I to III clinical trials referring to nicotine use disorder, cocaine use disorder, and methamphetamine use disorder, including both active and passive immunization products, were found after the primary search. Out of these 22 trials, only 7 have been identified as having published results in the secondary search. The vast majority of identified trials were phase II, targeting nicotine use disorder, using active immunization (NicVAX, NIC002, TA-NIC, NIC7-001/003, and SEL-068), and presented mixed results (18–20). The tolerability of these vaccines was good, but continuous abstinence was significant only in subjects with the highest serum antinicotine levels (19), or it was significant only in short term (20). No published results of phase III trials evaluating vaccines for nicotine use disorder were found (21–24).

Immunization for patients with cocaine use disorder (TA-CD, dAd5GNE) was explored in phase I and II clinical trials (33–36). Self-reported use of cocaine tended to decrease as a function of antibody titer in one trial (33), while in another trial subjects reaching high levels of serum IgG anti-cocaine antibodies ($\geq$43 μg/ml) had significantly more cocaine-free urine samples than those with low levels and those receiving placebo, during week 9–16 (35). Although yet another trial with TA-CD did not reach its primary outcome after week 8 more vaccinated than placebo subjects attained abstinence for $\geq$2 weeks, without reaching the significance level (34).

Immunotherapy for methamphetamine use disorder is still in its early phase, and passive immunization is the only clinically explored option (37–39). This therapy is based on human-murine chimeric monoclonal antibodies, which are considered able to bind methamphetamine with presumed high specificity and affinity (37–39). Unfortunately, no results of clinical trials are yet available to support this claim.

The evolution of the research in the field of immunotherapy for SUD is reflected by the development of second-generation investigational products. This progress was fueled by the need to find newer haptens and better carriers, able to induce more specific and intense immune responses, which translate to better efficacy. Also, adjuvants are important for triggering a persistent immune response, and new substances from this category are needed, besides aluminum.

In the case of anti-nicotine vaccines, the first generation of products used 3'-aminomethyl nicotine conjugated with Pseudomonas aeruginosa r-exoprotein in case of NicVAX, a non-infectious pseudo-viral particle (VLP) in case of NIC-002, or recombinant cholera toxin B (rCTB) subunit as transporter molecule for TA-NIC (18, 20). In the case of second-generation products, the transporter is represented by cross-reacting material (CRM) for NIC7-001, and a nanoparticle technology (targeted synthetic particles) for SEL-068 (25, 26). In the case of cocaine use disorder, the first-generation vaccine, TA-CD, used rCTB, while the newest investigational product, dAd5GNE, used the proteins of a modified adenovirus conjugated with a cocaine analog (33–36).

An overview of the trials presented in **Table 1** shows the need to find better defined primary outcome measures and to extend the duration of monitoring over 12 months. Also, trials with active comparators should be designed, and quantification of the patients' tolerability and quality of life during the study could also be useful.

CONCLUSIONS

The limited number of phase III clinical trials detected by this review ($N = 4$) indicates the need to re-evaluate the conceptual design of immune therapy in SUDs (**Table 2**). Despite the mixed, and mostly negative evidence of efficacy for the first-generation conjugate vaccines against cocaine and nicotine in clinical trials, second-generation vaccines are developing, thus renewing the potential clinical utility of active immunization in the treatment of substance use disorder (14). Even the first generation trials contained several positive results, but only in specific sub-populations, i.e., patients able to develop high levels of antibodies targeting the specific drug of abuse (19, 35). No significant tolerability and safety aspects were reported in trials with published results, which monitored the adverse events rate.

As limitations of the review, it is important to mention that no data about the current status of each investigational product were collected, as no such information has been found in the searched databases. Note releases from the manufacturers' sites regarding these products were not included in this review. Preclinical studies may be important to review, but this article was focused only on human trials.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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STUDY PROTOCOL
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The Feasibility and Utility of Harnessing Digital Health to Understand Clinical Trajectories in Medication Treatment for Opioid Use Disorder: D-TECT Study Design and Methodological Considerations

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Introduction: Across the U.S., the prevalence of opioid use disorder (OUD) and the rates of opioid overdoses have risen precipitously in recent years. Several effective medications for OUD (MOUD) exist and have been shown to be life-saving. A large volume of research has identified a confluence of factors that predict attrition and continued substance use during substance use disorder treatment. However, much of this literature has examined a small set of potential moderators or mediators of outcomes in MOUD treatment and may lead to over-simplified accounts of treatment non-adherence. Digital health methodologies offer great promise for capturing intensive, longitudinal ecologically-valid data from individuals in MOUD treatment to extend our understanding of factors that impact treatment engagement and outcomes.

Methods: This paper describes the protocol (including the study design and methodological considerations) from a novel study supported by the National Drug Abuse Treatment Clinical Trials Network at the National Institute on Drug Abuse (NIDA). This study (D-TECT) primarily seeks to evaluate the feasibility of collecting ecological momentary assessment (EMA), smartphone and smartwatch sensor data, and social media data among patients in outpatient MOUD treatment. It secondarily seeks to examine the utility of EMA, digital sensing, and social media data (separately and

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compared to one another) in predicting MOUD treatment retention, opioid use events, and medication adherence [as captured in electronic health records (EHR) and EMA data]. To our knowledge, this is the first project to include all three sources of digitally derived data (EMA, digital sensing, and social media) in understanding the clinical trajectories of patients in MOUD treatment. These multiple data streams will allow us to understand the relative and combined utility of collecting digital data from these diverse data sources. The inclusion of EHR data allows us to focus on the utility of digital health data in predicting objectively measured clinical outcomes.

Discussion: Results may be useful in elucidating novel relations between digital data sources and OUD treatment outcomes. It may also inform approaches to enhancing outcomes measurement in clinical trials by allowing for the assessment of dynamic interactions between individuals' daily lives and their MOUD treatment response.

Clinical Trial Registration: Identifier: NCT04535583.

Keywords: opioid use disorder (OUD), digital phenotyping, medication for opioid use disorder (MOUD), ecological momentary assessment (EMA), passive sensing, social media

INTRODUCTION

Across the U.S., the prevalence of opioid use disorder (OUD) and the rates of opioid overdoses have risen precipitously in recent years. Drug overdose has been called a "modern plague" (1) and is the leading cause of death of Americans under age 50, having surpassed peak death rates from gun violence, HIV, and car crashes (1, 2). Over 100,000 Americans died from a drug overdose from May 2020 to April 2021 (3). This dramatic spike in OUD has also been accompanied by marked increases in injection-related infections (including infective endocarditis and Hepatitis C) (4–7), babies born with Neonatal Opioid Withdrawal Syndrome (8) and healthcare and criminal justice costs (9).

Several effective medications for OUD (MOUD) have been shown to be life-saving including buprenorphine, methadone, and naltrexone products (10, 11), and to greatly increase opioid abstinence, reduce HIV/infectious disease risk behavior, and reduce criminality. Greater MOUD retention is associated with the most positive treatment outcomes (12–16). However, over 50% of patients receiving MOUD dropout of treatment within 3–6 months after treatment initiation (17–21), falling short of the longer threshold of treatment shown to offer sustained benefit (22, 23). Additionally, given the chronic relapsing nature of the disease of addiction, and inconsistent compliance with MOUD, many individuals continue to engage in opioid use during treatment, increasing the risk of overdose (24, 25).

Many factors predict attrition and continued substance use during substance use disorder (SUD) treatment (26, 27), including, stress, mental health comorbidities, continued exposure to high-risk social networks or contexts, and the neurobiology underpinning addiction. However, this literature has examined a limited set of predictors of outcomes in MOUD treatment and may not reflect a comprehensive understanding of treatment non-adherence (28). Further, treatment engagement is typically evaluated via structured clinical assessments conducted on an episodic basis and may not reflect factors in individuals' daily lives that impact their OUD treatment trajectories. Thus, there is tremendous opportunity to more frequently and extensively examine factors that impact individuals' clinical trajectories in MOUD in real time.

Digital methodologies offer great promise for capturing intensive, longitudinal ecologically-valid data from individuals receiving MOUD to extend our understanding of factors that impact treatment engagement and outcomes (29, 30). In particular, the use of digital devices such as smartphones or wearables that measure individuals' health-related behavior (sometimes referred to as "digital phenotyping") (31) has the potential to provide personalized health care resources. The ubiquity of digital devices and the explosion of "big data" analytics enable the collection and interpretation of enormous amounts of rich data about everyday behavior. This includes the use of digital devices to implement "ecological momentary assessment" (EMA) (32) in which individuals are asked to respond to brief queries on their mobile devices (assessing, for example, craving, mood, withdrawal symptoms, and pain). It also includes passive sensing data collected via sensors embedded in smartphones and/or wearable sensing devices such as smartwatches that provide information about the wearer's health (e.g., heart rate and heart-rate variability measured via wearable photoplethysmography), behavior (e.g., social contact via calls, texts and app use), and environment (e.g., location type via GPS) (33). And, it includes social media data that individuals produce (e.g., the images and the texts they post).

A rapidly growing literature is underscoring the utility of such digital health data-driven approaches to understanding human behavior (34–37). Digitally-derived data may similarly reveal new insights into the temporal dynamics between moderators and mediators of MOUD treatment outcomes. Such data may complement and extend data captured via structured clinical assessments and provide a more comprehensive understanding of each individual's course of treatment. And these data, in turn,

may increase our ability to develop more potent and personalized treatment models for OUD.

The developing literature on the application of digital health to understanding individuals' trajectories in SUD treatment has shown promise. One study that used EMA to identify predictors of substance use among adults after an initial episode of SUD treatment showed high EMA completion rates (81%) and identified specific substance use patterns, negative affect and craving as predictors of substance use (38). EMA research has also demonstrated differing relationships between drug triggers (e.g., exposure to drug cues or mood changes) and different types of drug use. Specifically, drug triggers increased for hours before cocaine use events but not before heroin use events (39). And, among smokers trying to quit, smoking lapses were associated with increases in negative mood for many days (and not just hours) (40).

Additionally, EMA research with adults in MOUD treatment demonstrated a stronger relationship between craving and drug use events than between stress and drug use events (41). EMA-assessed momentary pain has been shown to be indirectly associated with illicit opioid use via momentary opioid craving (42). Further, MOUD treatment dropout has been shown to be more likely among individuals who report more "hassles", higher levels of cocaine craving, lower levels of positive mood, a recent history of emotional abuse, and a recent history of being bothered frequently by psychological problems. It is noteworthy that none of those factors predicted individuals' non-compliance with completing EMA (43). Other EMA research revealed that patients in MOUD treatment who share similar patterns of drug use (frequent opioid use, frequent cocaine use, frequent dual use of opioids and cocaine, sporadic drug use, or infrequent drug use) tended to have similar psychological processes preceding drug use events (44).

Less research has focused on the utility of passively collected sensing data or social media data in predicting substance use. One study used GPS data from phones to assess exposure to visible signs of environmental disorder and poverty among adults in outpatient MOUD treatment. That study provided a proof of concept that digitally-captured environmental data could predict drug craving and stress 90 min into the future (45). Another study with adults in outpatient MOUD, focused on passive assessment of stress, showed that the duration of a prior stress episode predicts the duration of the next stress episode and that stress in the mornings and evenings is lower than during the day (46). And another study demonstrated that deep-learning analytic approaches applied to social media data may be useful in identifying potential substance use risk behavior, such as alcohol use (47).

Overall, these findings have provided some new insights into how data collected in naturalistic settings may enhance an understanding of risk profiles among individuals in SUD treatment. Nonetheless, the breadth of factors evaluated to date has been limited, and most digital health studies conducted with populations in SUD treatment have relied exclusively on self-reported clinical outcomes (with limited focus on objective metrics such as urine screens, medication fills, and clinical visits). Additionally, most studies have solely sought to predict substance use events.

This paper describes the protocol (including the study design and methodological considerations) from a novel study supported by the National Drug Abuse Treatment Clinical Trials Network (CTN) at the National Institute on Drug Abuse (NIDA). This study, referred to as "Harnessing Digital Health to Understand Clinical Trajectories of Opioid Use Disorder" (D-TECT; CTN-0084-A2) primarily seeks to evaluate the feasibility of collecting EMA, digital sensing and social media data among patients in outpatient MOUD treatment. It secondarily seeks to examine the utility of EMA, digital sensing, and social media data (separately and compared to one another) in predicting MOUD treatment retention, opioid use events, and medication adherence [as captured in Electronic Health Records (EHR), medical claims, and EMA data]. This is the first project to include all three sources of digitally derived data (EMA, sensing and social media) in understanding the clinical trajectories of patients in MOUD treatment. Multiple data streams will allow us to understand the relative and combined utility of collecting digital data from these diverse data sources. The inclusion of EHR data allows us to focus on the utility of digital health data in predicting objectively measured clinical outcomes.

METHODS AND ANALYSIS

Overview of Study Design

Individuals with OUD will be recruited for the study from among patients who are active in outpatient MOUD treatment with buprenorphine medication for at least 2 weeks at one of four Addiction Medicine Recovery Services (AMRS) programs at Kaiser Permanente Northern California (KPNC). Once it is confirmed that eligibility criteria are met, each participant will provide electronic informed consent and complete the baseline assessment by phone. The baseline appointments will take ∼2.0 h to complete, which will be done in two to three visits. Participants will be asked to wear a smartwatch and carry a smartphone (a study-supplied one or their own) that will passively collect sensor data. They will be asked to actively respond to EMA prompts through a smartphone 3 times daily and to self-initiate EMA responses daily if substance use occurred over the 12-week study. For those who consent to the optional social media component, social media data will be downloaded by the participant directly from the social media platform to a secure server using a remote desktop at the beginning of the study and again at the end of the study. EHR data extraction will occur at ∼16 weeks after the full study is completed and will collect data 12 months prior to EMA start (the date the participant began receiving EMA prompts) through 12-weeks after EMA start (84 days after the EMA start date). A follow-up assessment (∼45 min in length) will occur by phone ∼12 weeks after EMA start. A graphic overview of the study phases is presented in **Figure 1**.

Study Sites and Rationale for Site Selection

KPNC is a large, integrated health care delivery system with 4.3 million members, providing care through commercial

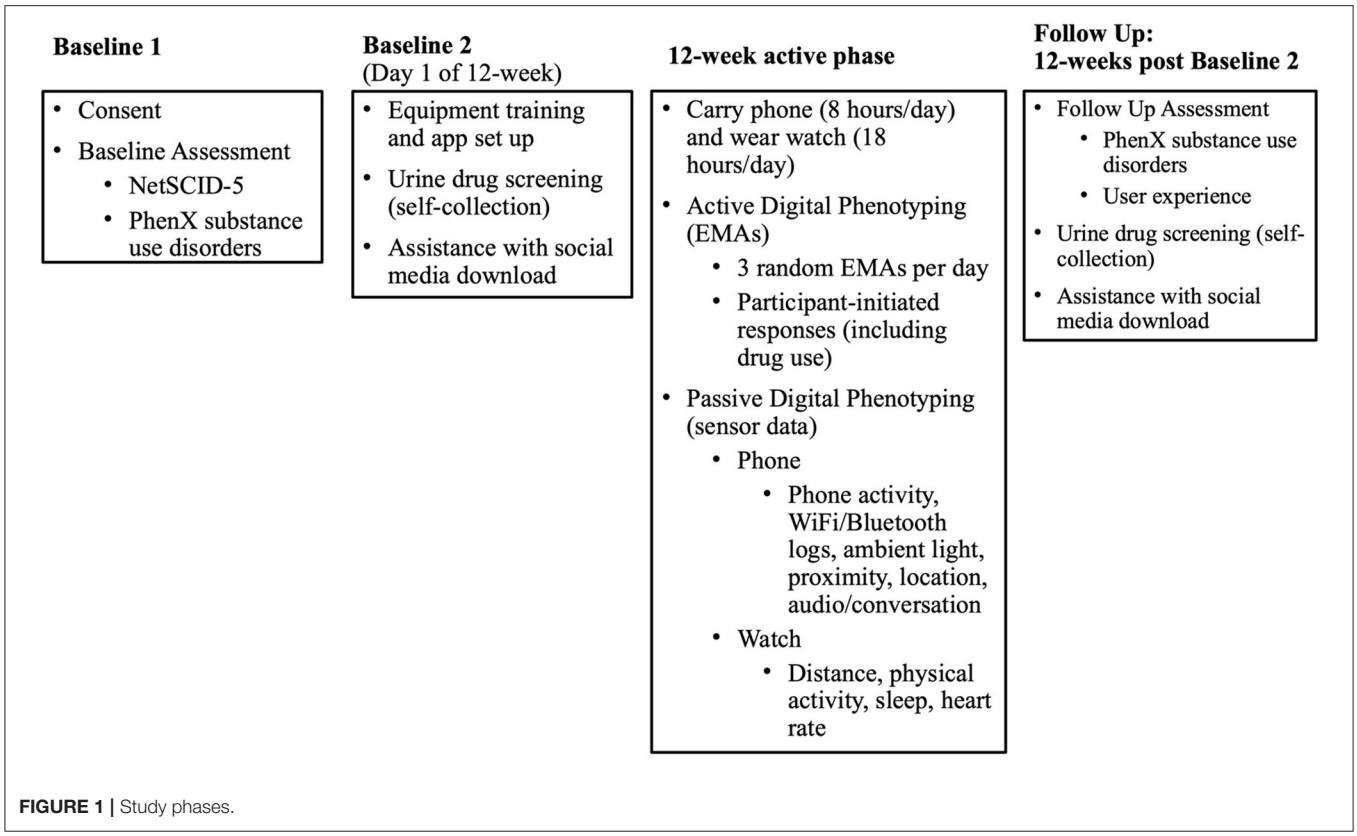

FIGURE 1 | Study phases.

plans, Medicare, Medicaid, and health insurance exchanges. It is comprised of a racially and socioeconomically diverse membership and is generally representative of the region's population with access to care. KPNC was selected based on its ability to (1) provide access to individuals who are prescribed buprenorphine for OUD and (2) provide access to EHR data on treatment retention, medication adherence, and service utilization. KPNC maintains a data repository, the Virtual Data Warehouse, which has combined EHR data (e.g., demographics, membership, diagnoses, service utilization, pharmacy, lab data) with several other data sources, including medical claims data (e.g., non-Kaiser pharmacy data).

The AMRS programs at KPNC offer a broad range of services, including prescribing buprenorphine for OUD, medical services, group and individual therapy, and family therapy. Staffing includes physicians, therapists, medical assistants, nurses, and social workers.

Participants

Participants will include individuals aged 18 years or older across all racial and ethnic categories. Eligibility criteria include: active in KPNC outpatient treatment and prescribed buprenorphine for OUD for the past 2 weeks (and attended at least one visit at AMRS in past 35 days); $\geq$18 years old; capable of understanding and speaking English; able to participate in the full duration of the study (12 weeks); have an active email account and willing to provide its address to researchers; permit access to EHR data; willing to carry and use a personal or study-provided smartphone for 12 weeks; and willing to wear a smartwatch continuously (except during pre-defined activities such as showering) for 12 weeks. Individuals will be excluded if they are: unwilling or unable to provide informed consent; currently in jail, prison or other overnight facility as required by court of law or have pending legal action that could prevent participation in study activities. We expect to recruit 50–75 participants.

Study Procedures

Recruitment and Screening

Potentially eligible patients will be initially identified from EHR data as meeting study criteria; eligibility is further confirmed through chart review. Eligible patients will be sent an invitational recruitment letter through a secure email message. Within approximately a week of mailing recruitment letters (or sending a secure email message), research staff will contact participants by phone to determine if they are interested and eligible, using the IRB-approved recruitment script, verbal consent form and final screening questions. If the individual is interested and eligible, research staff will schedule them for an initial baseline phone appointment and email them consent documents for their review before their appointment.

Informed Consent

Informed consent will be obtained by phone and documented online using an electronic signature. Each participant will be asked to pass a brief consent quiz to document comprehension of the study activities. The research staff will obtain authorization

from participants for use of protected health information, such as their EHR and medical claims data.

Baseline

The baseline process will be conducted in two or three phone appointments: the first appointment will consist of informed consent and the baseline assessment (Baseline 1), and the second (and third, if necessary) appointment (Baseline 2/3) will consist of a urine drug screen, setting up study devices, installing study applications ("apps"), and learning to use devices and apps (**Figure 1**).

The baseline assessment consists of interviewer-administered measures (described below) examining participant characteristics, current substance use (e.g., tobacco, alcohol, opioids, and other drugs), substance use and mental health disorders, and the impact of the COVID-19 pandemic. Once the first baseline appointment is completed, participants will be mailed a urine drug screen kit, a smartwatch and study smartphone (if applicable) and technology training documentation.

Once the equipment is received, research staff will schedule a second phone appointment with each participant to review the urine collection and technology training documentation. Research staff will walk through the set-up, use and care of the smartphone and smartwatch, installation of the study app and the Garmin Connect app (described below) if they are not already installed on a study-provided phone, as well as instructions for initiating and completing the daily EMA surveys. Research staff will also instruct participants to collect a urine sample and upload results.

Participants who consented to the social media part of the study will also receive instruction on how to request and download their social media data.

Active Study Phase (12-Weeks)

During the active 12-week study phase, the research staff will monitor participant compliance using a custom dashboard (e.g., their EMA completion rate and whether they carry the study phone and wear the study watch). In the first 2 weeks, participants will be followed closely. If after a 48-h period there are no EMA data, and/or no phone carry time data, and/or no watch wear data, research staff will follow-up directly with the participant via phone, text, and/or email to encourage the participant to continue their participation and/or troubleshoot any problems that may arise with the smartphone, smartwatch, and/or study app. All participants will have a 1-week check-in appointment via phone with research staff to review the participant's experience, review data collection over the past week, and answer any questions or resolve any technical issues with the study devices (regardless of device carry/wear time compliance or EMA completion rate). Thereafter, research staff will send weekly check-in texts or phone calls unless there is a 48-h period of no EMA data, and/or no phone carry time data, and/or no watch data. In those instances, the research staff will attempt to reach the participant by phone, text, and/or email. The research staff will make up to three contact attempts prior to engaging alternate contact(s).

Engagement in Research

To be considered engaged in the study, an individual must respond to a minimum number of EMA prompts (complete at least 2/3 of the EMA surveys per day on 7 out of the first 14 days) and record at least 8 h of smartphone/smartwatch sensor data per day on 7 out of the first 14 days of study participation. If an individual does not meet the engagement criterion and is non-responsive to research staff outreach in the first 14 days of study participation, then the individual will be considered a "non-engager" and the study team will continue to recruit until the targeted sample size is met. Non-engagers will not be withdrawn from the study, as we will attempt to collect all possible data from all participants.

Follow-Up

A follow-up assessment will be completed by phone ∼12 weeks post-EMA start. Research staff will administer an interviewer-based assessment to measure current substance use, participant experience with the study devices, treatment utilization, reasons for drop out (if appropriate), employment, insurance coverage, medication use/dose (if applicable), and overdose (if applicable). Participants will be mailed a urine drug test kit and asked to collect another urine sample and upload test results. Participants who consented to the social media part of the study will be asked to request and download their social media data a second time.

Description of Measures

A summary of the clinical assessments and digital health assessments to be conducted in this study are reflected in **Figures 2**, **3**, respectively. Brief descriptions of each of these measures is provided below.

Prisoner Status Assessment: An individual's prisoner status must be assessed for each participant at each separate encounter, as this study will not apply for Office of Human Research Protection (OHRP) Prisoner Certification. An **Inclusion/Exclusion** form will be used to obtain information on inclusion and exclusion criteria to document eligibility. **Locator Form.** A locator form is used to obtain information at baseline and each contact to assist in finding participants throughout the study. This form collects the participant's current address, email address, and phone numbers. **PhenX Substance Abuse and Addiction Core Tier 1 (PhenX Core Tier 1).** The PhenX Core Tier 1 is a part of the Substance Abuse and Addiction Collections (48) that are being adopted across multiple studies funded by NIDA. This study will use the following subset of measures from the Core Tier 1: demographics (age, ethnicity, gender, race, current educational attainment, current employment status, and current marital status) and current substance use (tobacco, alcohol, and drugs) (49). The demographics (except for employment status) will only be collected at baseline, while current substance use and current employment status will be collected at baseline and follow-up. **The PhenX Substance Abuse and Addiction Core Tier 2** (PhenX Core Tier 2). The PhenX Core Tier 2 is a complementary set of 8 measures to the PhenX Core Tier 1 (i.e., annual family income, child-reported parental education attainment, family history of substance use problems,

Study Visit	Measures	Data Collection Method
Screening	• Verbal consent • Prisoner Status Assessment (repeated at each study visit) • Inclusion/Exclusion Form	• Interview
Baseline 1-3	• Prisoner Status Assessment • Electronic Consent (eConsent) • Electronic Health Insurance Portability and Accountability Act (eHIPAA) Authorization • Consent Quiz • Locator Form (completed at each call) • Phenotypes and eXposures project measures (PhenX) Core Tier 1 (demographics & current substance use) • PhenX Core Tier 2 (annual family income) • National Survey on Drug Use and Health (NSDUH) (annual family income)* • Baseline Assessment - COVID-19 (impacts due to the pandemic) • NetSCID-5 (computer-based Structured Clinical Interview for DSM-5 – research diagnosis) • Urine Drug Screen (UDS) (recent use)	• Interview
	• Social Media (images/texts of postings & comments, reactions, date/time)	• Download (from social media platform via remote desktop)
Follow-up	• Prisoner Status Assessment • PhenX Core Tier 1 (current substance use) • Follow-up Assessment (participant experience; employment; treatment utilization; insurance coverage) • UDS (recent use)	• Interview
	• Social Media (images/texts of postings & comments, reactions, date/time)	• Download (from social media platform via remote desktop)
	• Electronic Health Record (EHR)	• Extraction**
	• Medical Claims	• Extraction**

FIGURE 2 | Table of study assessments. *NSDUH is only collected for participants who are unsure of the total family income. We will use as subset of questions to determine which income category best characterizes total combined family income. **EHR/Medical Claims data will be extracted by the data analyst ∼16 weeks after completion of study and includes data 12 months prior to EMA start through 12 weeks post-EMA start.

household roster-relationships, internalizing, externalizing, and substance use disorders screener, occupation/occupational history, peer/partner substance use and tolerance of substance use, and social networks) (50). This study will only use a subset of questions from the Annual Family Income measure to get an estimate of total income of all family members (49). If the participant is unsure of the total family income, then we will use a subset of questions from the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health (NSDUH) survey to determine which income category best characterizes total combined family income (51). These measures will be securely, electronically stored in a REDCap database.

NetSCID-5: The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview designed to assess substance use and mental health diagnoses (52). This study will use an electronic version of the SCID-5, the NetSCID-5, developed by TeleSage. The TeleSage NetSCID-5 is fully licensed by the American Psychiatric Association and has been validated (53). TeleSage has the capability of customizing

Device	Measures	Data Collection Method
Smartwatch	• Ambulatory Physiological Assessment using Mobile sensing (distance; physical activity; sleep; heart rate)	• Wearable*
Smartphone	• Passive Assessment using Mobile Sensors (phone activity; WiFi/Bluetooth logs; ambient light; proximity; location; audio/conversation)	• Carryable**
	• Ecological Momentary Assessment (EMA) (including self-report of drug use)	• Self-report***
	• Momentary Self-Regulation Scale 12-item	• Self-report***

FIGURE 3 | Active study phase digital health assessments. *Wear smartwatch at least 18 hours per day, data transmitted real-time for 12 weeks. **Carry smartphone at least 8 hours per day, data transmitted real-time for 12 weeks. ***3 times per day for 12 weeks.

the NetSCID-5 measure, and modules relevant for this study include: bipolar I disorder, major depressive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, adult attention deficit hyperactivity disorder, alcohol use disorder, and other use disorders [cannabis, stimulants/cocaine, opioids, phenylcyclohexyl piperidine (PCP), other hallucinogens, inhalants, sedative-hypnotic-anxiolytic, and other/unknown]. The TeleSage NetSCID-5 will be administered by research staff who are trained and credentialed to conduct this diagnostic assessment.

Urine Drug Screen: Urine drug screen kits will be mailed to participants, and participants will be asked to collect a urine sample and then record and upload its results using a secure system (e.g., REDCap) at first baseline appointment and at follow-up. All urine specimens are collected using CLIA-Waived and FDA-approved one-step multi-drug screen test cups following the manufacturer's recommended procedures. The study will use the DrugConfirm Advance Urine Drug Test Kit that screens for: alcohol, amphetamine, barbiturate, buprenorphine, benzodiazepine, cocaine, fentanyl, MDMA (ecstasy/molly), methamphetamine, methadone, morphine 300 ng/mL, oxycodone, phencyclidine (PCP), tramadol and delta-9-tetrahydrocannabinol (THC).

In order to reduce risks of substituted or adulterated urine samples, the research staff will conduct the study urine drug screens in real-time (i.e., reviewing collection instructions and walking the participant through the entire process via phone) during the Baseline 2 phone appointment. Participants will send a photo of the temperature strip to research staff immediately after they produce the sample to ensure the temperature is within the specified valid temperature range of 90°-100°F. Additionally, we will ask participants take photos of the test result strips and send the photos of the results securely to research staff in real-time (while the participant is still on the phone). Research staff will review the photos that are sent to ensure that the results captured within the photos are legible and not blurry or otherwise indecipherable.

Digital Health Technology

Ambulatory Physiological Assessment Using Mobile Sensors

We will develop a smartphone application ("study app") for both Android and iOS devices. The study app can sense and store contextual information about a participant, e.g., location, physical activity (step count), conversation duration and count (non-identified audio information such as segments of silence, and speech features such as pitch control and voice quality), app usage, call/text, screen on/off, phone lock/unlock, and phone notifications (54). Features will be derived from the raw sensor streams to create multiple relevant contextual variables. This custom application will be installed directly on the study-provided smartphone (Moto G7 Power and/or Moto G Power) or on a participant's smartphone if they have a compatible phone (iPhones, running iOS 12 or higher or Android devices running Android 8.0 or higher with at least 2.5 GB RAM and 4 GB of available storage).

In addition to the smartphone, participants will be provided with a smartwatch (Garmin Vivosmart 4). The participants will be asked to wear the smartwatch continuously (except during pre-determined exception periods, such as when the participants are showering or charging the device). The Garmin Vivosmart 4 smartwatch is comfortable, lightweight, and has a long battery life of up to 7 days (55) and an easy-to-use interface. The device can continuously collect and track a variety of sensor data in the background, as long as the user is wearing the device. The data from the wearable is synced directly with Garmin cloud servers,

using the "Garmin Connect" application installed on the phone, and we will not have direct access to the raw sensor data. We will use the Garmin Health Connect API to get various health metrics that are computed by Garmin's proprietary algorithm, such as heart rate, sleep stage information (i.e., periods and events of light/deep sleep), stress levels, and physical activity levels (including energy expenditure) and step counts). Through the Garmin Health Connect API, Garmin's servers will push the various metrics computed from the raw data to the storage servers at Dartmouth College.

Ecological Momentary Assessment

Participants will be prompted 3 times per day over 12 weeks by the smartphone app to self-report sleep, stress, pain severity, pain interference, pain catastrophizing, craving, withdrawal, substance use risk context, mood, context, substance use, self-regulation, and MOUD adherence (41, 56–59). The EMA prompt delivery times will be randomized within each of the prompt timeframes (e.g., morning, mid-day, end of day). In addition to prompted EMAs, participants will be asked to self-initiate EMA responses if substance use occurred (e.g., opioids, cocaine, or other stimulants). When determining the rate of completion of self-initiated reports of substance use, we will be able to cross-reference responses to the following question asked in the "End of the Day" EMA prompt ("Did you use any drugs at all today without reporting it?") with participant's self-initiated substance use EMA data.

Additionally, participants will be asked to complete a **Momentary Self-Regulation Scale**[1] via EMA. This brief 12-item questionnaire assesses self-regulation on a momentary basis as individuals move through their daily lives. This information will be collected 3 times daily over the 12-week study period by smartphone.

Social Media

Participants will be asked to request and then download their social media data (Facebook, Instagram, or Twitter) to a secure server using a remote desktop application. These three social media platforms provide the functionality for each user through their account setting to download their social media data as an aggregated structured file. After requesting a data download from a social media website, the participant will receive an email notification when the downloadable copy of the data has been created—typically in <48 h from the request. Once the social media data are ready to download, the participant will log into a remote computer located at Dartmouth College by using Microsoft Remote Desktop and will download their social media data to the secure research study computer. After completing the download, the participant will sign out of the remote computer and alert the research team. Images and text postings as well as date/time for each post will be extracted from the downloaded social media data. As noted elsewhere, participation in this part of the study is optional; participants can still participate in the study and decline to provide their social media data.

We will parse the JSON/JS files of the downloaded social media data to extract the information of interest, including posting date, text, and corresponding image paths on a local storage. We will aggregate the extracted data into a pickle file composed of different data dictionaries for text, posting dates, and local image paths. It is noteworthy that all the social media data from three variant platforms will be in the same format after processing. We plan to collapse and aggregate the data collected across the three social media platforms to reduce data sparsity and thereby increase the number of study days that are represented in the training and evaluation data sets.

EHR Data

EHR data extraction will include all outpatient and inpatient encounters, medications, procedures, and diagnoses for the 12 months prior to EMA start and the 12-week study period. In addition, we will extract lab results from urine drug screens, patient demographic information, KPNC health plan membership status, and insurance deductible level. We will extract appointment data to determine if visits were canceled or missed. KPNC is also an insurance plan and has claims data on non-KPNC services that were submitted as medical claims for reimbursement.

Clinical and Safety Assessments

Clinical and safety events may be elicited at baseline or spontaneously reported to study staff at any encounter following consent. Safety events suggesting medical or psychiatric deterioration will be brought to the attention of the study clinician for further evaluation and management.

Compensation

Participants will be compensated up to $21 per week for completing EMA surveys, up to an additional $10 per week bonus for completing a minimum of 80% of received EMAs, and up to $14 per week for carrying their smartphone at least 8 h per day and wearing the smartwatch at least 18 h per day. At the end of the 12-week active phase of the study, participants will receive a $50 bonus for either using their personal smartphone or returning a study-provided smartphone, and a $50 bonus for returning the study-provided smartwatch. Finally, participants who consent to the social media portion of the project will receive up to an additional $180. Total possible compensation will be up to $820 over the course of the 12-week active study phase for the digital data collected (i.e., each EMA completed plus EMA bonus, smartphone carry time met and smartwatch wear time met, and social media data download, if applicable). In addition to the earnings and bonuses (described above), an individual who completes a minimum of 80% of received EMA surveys within a given week will qualify for a drawing at the end of that week where the individual could win a $50 prize. Each individual will have an opportunity to participate in up to 12 drawings over the 12 weeks. During the 12-week active study phase, any incentives, bonuses, and/or drawings earned will be uploaded weekly to a reloadable debit card. Study participants will be compensated

[1] Scherer EA, Kim SJ, Metcalf SA, Sweeney MA, Wu J, Xie H, et al. The development and validation of a momentary self-regulation scale. *JMIR Mental Health* (under review).

$75 for completing the baseline appointments and baseline urine drug screen (via Target gift card), and $100 for completing the 12-week follow-up appointment and follow up urine drug screen (via Target gift card). Total compensation will be up to $995 for participating in all study activities [digital compensation ($820) plus baseline and follow-up appointment compensation ($175)].

Statistical Analyses

Primary and Secondary Outcomes (Endpoints) and Hypotheses

The primary outcomes will include (1) the percentage of days during the 12-week active phase enrolled participants met criteria for wearing the smartwatch and carrying the smartphone; (2) the response rate to EMA prompts during the 12-week active phase; and (3) the percentage of participants who consent to social media data download and sparsity of social media data per participant. We hypothesize that the majority of participants who enroll in the study will wear the smartwatch, carry the smartphone, respond to EMA prompts, and be willing to share their social media data with the research team. We expect the number of participants deemed "non-engagers" will be low.

The secondary outcome measures will be (1) OUD treatment retention (days retained in OUD treatment program) based on EHR data; (2) days covered on MOUD based on EHR and EMA data; and (3) non-prescribed opioid use based on EHR and EMA data. We hypothesize that intensive longitudinal digital data capturing patient context and psychological state will be useful for predicting treatment retention, opioid use events and buprenorphine medication adherence.

Statistical Methods

For our primary feasibility assessment for primary and secondary outcomes, we will generate descriptive statistical summaries of the level of adherence of study participants to the desired protocol (e.g., EMA response rate, smartwatch wear rate and smartphone carry rate).

For our predictive analyses for primary and secondary outcomes, we are interested in measuring and predicting outcomes that may occur repeatedly over a 12-week observational period (e.g., patterns of daily drug use) using digital health technology. In digital health the spatio-temporal granularity of information about an individual is of higher resolution than that obtained through cross-sectional or traditional longitudinal studies (60). We will therefore assess the utility of using data from smartphones, smartwatches, social media, and ecological momentary assessment to predict, explain and detect these outcomes.

Our approach to prediction will include regression methods (e.g., logistic regression), but we will also use various machine-learning approaches for binary classification (e.g., random forest, support vector machines, K-means, gradient boosted trees, neural networks). For each of these classification techniques, we will assess the utility of the various digital data for improving prediction quality.

The study will generate the nested longitudinal data with binary response sequences collected over time. The regression model (logistic regression) will be built to account for the nested data structures by incorporating both fixed effects and random effects, which would allow us to examine both inter and intra-individual differences. Machine learning models can also be integrated with the random-effects structure as in the mixed-effect models (61). In the cross-validation, the training data will be split into k-folds by patient id. Previous work has shown that whether training data is split by record or by patient can significantly affect model performance (62), with better performance typically being achieved when splitting data by record rather than by participant.

For social media data, we will use deep neural networks for feature extraction and predictive analysis. Specifically, pretrained residual neural network (ResNet) (63) will be used to extract features from images and bidirectional encoder representations from transformers (BERT) (64) models will be used to extract features from text. Using these neural networks, social media images and text can be represented as dense vectors that can be aggregated with the rest of the collected data for predictive analysis. We will also explore classic machine-learning methods (such as random forest, support vector machines, and gradient boosted trees) for social media-based prediction, and compare their results to the performance of deep neural networks. Typical evaluation methods used to assess the prediction quality include area under the receiver operating characteristic curve (AUROC), accuracy, precision, F-score, sensitivity (recall), and specificity. The relative utility of the various data for predicting outcomes will be assessed at two levels - individual features and aggregated features (e.g., Facebook, Twitter, GPS, step, sleep, mood). The contribution of each feature in predicting the outcome variable will be assessed using a model-agnostic machine-learning approach to reverse-engineering algorithms by perturbing model inputs based on game theory, SHapley Additive exPlanations (SHAP) (65, 66).

When missing data are encountered, we will apply domain knowledge to reflect on the probable reasons that the data are missing. Based on our knowledge-based assessment of the nature of the missing data, missing samples will be imputed using appropriate imputation methods (67, 68).

There are at least two approaches to integrating data from the three data sources for use by a single prediction model, depending on whether the prediction models operate in a lower-dimensional "latent/embedding space" or a higher-dimensional "feature space". Deep learning models typically operate in the latent/embedding space, while other machine learning models (e.g., Random Forest, Gradient Boosted Regression Tree) operate in the feature space.

When combining data in the feature space, features must be engineered from both structured and unstructured data. The unstructured social media data, in particular, may require manual or automated annotation in order to generate features. When combining data in the latent space, models that convert both structured and unstructured data into the latent space will be required. These models could be pre-trained on other similar data sources (e.g., BERT for natural language text, pre-trained ResNet model on ImageNet for image data, Activity2Vec for sensor data). We are not aware of pre-trained models for generating embeddings from EMA/survey data.

Yet another approach for "integrating" all 3 data sources is to train separate models using each dataset and an ensemble predictor that combines the predictions from each model to generate a final prediction, e.g., bagging or accuracy-weighted ensemble (69).

We will perform k-fold cross validation (CV) when evaluating the performance of the prediction models. We will do a group k-fold CV where instead of randomly splitting all data into k-folds, we will divide our dataset into k groups such that each participant is assigned to only one group with no overlap between the groups. This is to prevent any data leakage that might happen due to a participant's data being present in the train and test sets.

This is an exploratory pilot study. Therefore, a detailed analysis of statistical power to detect effects was not performed. As we are predicting daily outcomes (e.g., daily medication adherence, daily drug use), the sample size that is potentially available to us is equal to the number of participants multiplied by the number of study days. For example, assuming 60 participants in the study, and a study period of 12 weeks (i.e., 84 days), the analytic sample size would be $60^*84 = 5{,}040$ participant-days. If the observed incidence of non-adherence or drug use is 10%, then we would observe ∼504 non-adherence or drug use events. Results of this study may generate a data set that could be helpful for future researchers to estimate the likely power of predictive models for this patient population, using similar sources of data.

DISCUSSION

In a world that is rapidly embracing digital health approaches to understand and provide resources to support health behavior, this study is distinct in that it will be the first to systematically assess the feasibility and utility of digitally-derived data from EMA, passive sensing and social media, all collected from the same sample of individuals in MOUD treatment. Results from this study may be useful in elucidating novel relations between digital data sources and treatment outcome. It may also inform approaches to enhancing outcomes measurement in clinical trials by allowing for the assessment of dynamic interactions between individuals' daily lives and their MOUD treatment response. It may additionally inform specific digital data collection protocols in the next phase of this line of research, including the need to abbreviate EMA questions to capture those most clinically useful and/or strategies for addressing any privacy or data sharing concerns that may arise among participants. As the opioid epidemic and opioid overdoses surge in the U.S., this novel study and its clinically-relevant implications are timely.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) at Kaiser Permanente Northern California (the single IRB overseeing this study). The patients/participants provided their written informed consent to participate in this study. We plan to disseminate findings from this research at scientific meetings and in multiple peer-reviewed publications, including results of analyses assessing the feasibility of using EMA, digital sensing and social media data among adults in outpatient MOUD and analyses assessing the predictive utility of these data sources in predicting MOUD treatment retention, opioid use events, and medication adherence.

AUTHOR CONTRIBUTIONS

LM, CC, C-HC, SH, DK, CL-H, and CS were responsible for developing the study design for this project. LM wrote the initial draft of the protocol paper. AA, CC, MD, MJ-M, HJ, CL-H, and BM were involved in study coordination and operations. GS was the study's Scientific Officer. SA, CL-H, VM, and WW prepared the data sets for analyses. NJ consulted on the statistical analysis plan. C-HC, ZL, VM, and WW conducted the statistical analyses. EH prepared the references. All authors participated in the review and revision process and approved the submission of this version of the protocol paper.

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REVIEW
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Switzerland's Dependence on a Diamorphine Monopoly

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In 2021, the manufacturer of diamorphine reported a possible impending shortage for Switzerland and Germany. This led us to investigate this controlled medicine's manufacture, market, and regulatory constraints. Based on our analysis of legal texts and gray literature in the form of reports and documents, we propose recommendations to prevent and address diamorphine shortages in Switzerland. Diamorphine, also known as pharmaceutical "heroin," is used medically to treat persons with severe opioid use disorder in a handful of countries. The controlled medicine is manufactured from morphine, which, in turn, is extracted from opium poppies. Studying data from the International Narcotics Control Board for 2019, we find that Switzerland accounts for almost half of the worldwide medical consumption of diamorphine. It manufactures more than half of the worldwide total and keeps the largest stocks. Moreover, Switzerland is dependent on a sole supplier of diamorphine (monopoly). As a niche product, diamorphine has an increased risk of shortage. Such a shortage would immediately threaten a valuable public health program for around 1,660 Swiss patients. We believe it is urgent to curtail the monopoly and ensure a stable supply for the future.

Keywords: diamorphine, Switzerland, market, manufacturing, shortages

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INTRODUCTION

Diamorphine, also known under its old brand name Heroin, is one of the most controversial substances worldwide. According to the 1961 Single Convention, it is a schedule I drug, meaning it is subject to the highest degree of control (1). In Switzerland, diamorphine is classified as a prohibited controlled substance (schedule d), but it can be used as a medicine under particular conditions (2).

Indeed, the Swiss Agency for Therapeutic Products (Swissmedic) approved diamorphine (under the brand name Diaphin) for treating persons with severe opioid use disorder in 2001 (3). Treatment with diamorphine prescription (TDP) is the only approved effective alternative for persons who do not respond to classic opioid agonist treatments (OAT), such as methadone or buprenorphine treatment (4, 5). It was introduced in 1994 in Switzerland as a pragmatic solution to an AIDS crisis and open drug scenes (6). Under heavy criticism at first, it is now enshrined in Swiss law (6) and recognized internationally as a successful and cost-effective public health program (5, 7, 8). In 2019, 1,663 persons in Switzerland received TDP, which has been reimbursed since 2002 by health insurers (6, 9).

In Switzerland, DiaMo Narcotics GmbH holds the marketing authorization for the only three diamorphine products available: Diaphin i.v. (intravenous), Diaphin IR (immediate-release) tablets, and Diaphin SR (slow-release) tablets (3). DiaMo Narcotics GmbH sources the active ingredient,

diamorphine, from two active ingredient manufacturers (10). Two other contract manufacturers then formulate the active ingredient: One contract manufacturer formulates Diaphin i.v., whereas Diaphin IR and SR tablets are formulated by another (10). Due to the small order volume, finding another contract manufacturer is not a realistic option, as noted by a report which analyzed the diamorphine supply situation in January 2021 (10).

In theory, other opioid products could constitute alternatives to diamorphine, but none so far have been authorized for this indication.

The 2021 Diamorphine Supply Disruption

The risk of a diamorphine shortage was already identified in 2016 by the Swiss Federal Council (11). In November 2020 the risk of a supply shortage of Diaphin i.v. became acute, due to the bankruptcy of the contract manufacturer, which formulated Diaphin i.v.: Legacy Pharmaceuticals (10). There were no stocks of Diaphin i.v. because of past difficulties with the contract manufacturer (10).

The impending shortage was not made public, and communication was restricted to the involved Swiss authorities and TDP centers. According to a report on the Swiss TDP, the communication regarding the supply was not transparent enough (10). In contrast to Swiss authorities, the German Medicines Agency announced an impending supply disruption of Diaphin i.v. for the German market in March 2021 (12). Based on publicly available information it is not possible to know if the bankruptcy of Legacy Pharmaceuticals also caused the German Diaphin i.v. supply disruption.

Shortages of diamorphine pose a significant problem for people in TDP and their treating physicians. Risks associated with treatment discontinuation are poorer mental and physical health, increased illegal activities, and consumption of illicit substances (13). Hence, a rapid solution is needed to supply the affected population in case of a shortage.

Structure of the Article

This article describes Switzerland's dependence on a diamorphine monopoly. We analyzed legal texts and gray literature in the form of reports and documents from Swiss and other authorities. Furthermore, we used reports and data from the International Narcotics Control Board (INCB).

Section "How Did Diamorphine Become a Niche Product?" will describe how the once widely used diamorphine has become a highly regulated niche product. The manufacturing and diamorphine market will be analyzed in sections "How Is Diamorphine Manufactured?" and "How Is the Market for Diamorphine Structured?" In section "Are There Legal or Regulatory Constraints Preventing the Introduction of a Diamorphine Generic in Switzerland?" we identify relevant regulations for diamorphine manufacturers in Switzerland. In section "How Did Switzerland Address the 2021 Supply Disruption?" we analyze the response to the 2021 supply disruption in Switzerland and compare it to the United Kingdom (UK). Lastly, we formulate actionable recommendations in section "What Do We Recommend?"

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HOW DID DIAMORPHINE BECOME A NICHE PRODUCT?

Under the brand name heroin, Bayer started commercial production of pharmaceutical diamorphine in 1898; a few years later, other pharmaceutical companies started offering diamorphine as well (14). In the late nineteenth century and early twentieth century, diamorphine was widely used and marketed for "heavy coughs, to relieve the pain of childbirth and serious war injuries, prepare patients for anesthesia, and control certain mental disorders" (15). At the turn of the century, addiction caused by diamorphine was first recognized as a problem; the first so-called "morphine maintenance clinics" were set up to treat persons with opioid use disorder (16, 17).

Internationally, the 1912 International Opium Convention aimed to control opiates strictly but was not implemented globally due to the outbreak of World War I (17). Diamorphine production was limited after the 1931 Geneva Convention established constraints and many countries banned the substance (16, 17). In 1961, the Single Convention on Narcotic Drugs replaced previous treaties and is in its revised version still in force today (1, 18).

At a national level, the United States (US) passed the Harrison Act in 1914, introducing federal narcotics controls (14, 16, 19), followed by an outright ban on diamorphine in 1924 (16, 19).

In contrast, in the United Kingdom (UK), the 1926 Rolleston report laid the groundwork to continue administering morphine or diamorphine to treat persons with an opioid (heroin) use disorder who did not respond to abstinence-based programs (20, 21). The so-called "British system" remained intact until the passing of the Dangerous Drugs Act in 1967, which restricted the right to prescribe diamorphine to specifically licensed doctors only (22). This led to a decrease in people treated with diamorphine (23–25). Clinical guidelines published in 1984 cemented the shift from injectable diamorphine to oral methadone prescription (22). Interestingly, the UK remains the only country in the world to also use diamorphine for severe pain associated with surgical procedures, myocardial infarction, or pain in the terminally ill, and for the relief of dyspnea in acute pulmonary edema (26).

Switzerland passed its first narcotics law that introduced an authorization requirement for manufacturing and trading opiates and cocaine in 1924 (27). Still in force today is the Federal Act on Narcotics and Psychotropic Substances (NarcA), which was passed in 1951 (28). It has often been revised, with the last major change dating to 2011 when the four-pillar policy (prevention, therapy, harm reduction, repression) and TDP were enshrined in the law. Aside from Switzerland, TDP is currently only available in Denmark, Germany, Luxembourg, the Netherlands, the United Kingdom, and Canada (29).

In conclusion, after being widely used, diamorphine is nowadays a niche product in few countries with low production volumes, putting it at high risk of shortage.

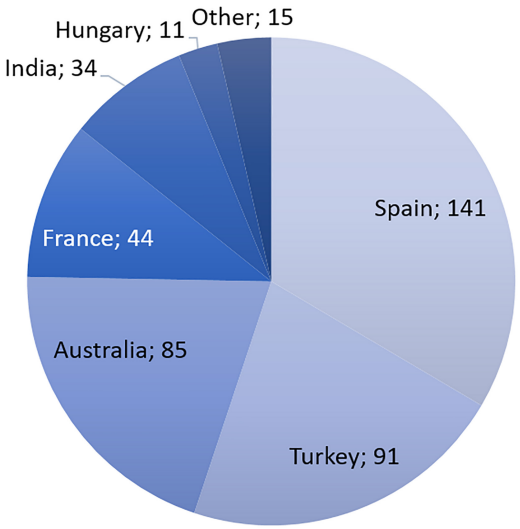

FIGURE 1 | Production of opiate raw materials rich in morphine in tons of morphine equivalent, 2019. Based on data from INCB technical report 2020.

HOW IS DIAMORPHINE MANUFACTURED?

The licit manufacture of diamorphine starts with the cultivation of poppy plants (Papaver somniferum) on licensed fields (30). Papaver somniferum contains, among other alkaloids, morphine, codeine, and thebaine (31). All three are chemically related and easily convertible into one another (31). Breeding allowed for the creation of varieties that yield higher amounts of morphine or other opioid alkaloids (31).

According to the INCB, the main licit cultivation countries are Australia, France, Hungary, India, Slovakia, Spain, and Turkey (**Figure 1**) (32). In 2019, Spain was the largest producer of morphine-rich raw materials (141 metric tons), followed by Turkey (85 metric tons), Australia (85 metric tons), and France (44 metric tons). Taken together, these four countries were estimated to account for 91% of the licit global production of morphine-rich raw materials in 2020.

The fully matured poppy plants' field-dried leaves, stalks, and seedpods are used to make poppy straw concentrate (1). In the next step, morphine is extracted from the poppy straw concentrate before reacting with either acetic acid or acetic anhydride to produce diamorphine. Pure diamorphine, both as a base and as a hydrochloride salt, is a colorless crystalline solid (33). All currently available diamorphine preparations for injection are lyophilized powders because an aqueous solution is not chemically stable enough for storage (34).

Whilst opiates are still manufactured from the opium poppy, advances in synthetic biology enable the creation of a yeast strain capable of making morphine from glucose (35). Four groups of researchers introduced different genetic components into the yeast genome, which combined constitute the entire morphine synthesis pathway (36–41). A morphine manufacturing yeast strain could change the current supply chain, as the manufacture of morphine by self-replicating yeast might be cheaper and more stable than the current processes. However, to the best of our knowledge, no morphine product using this technology has entered the market.

Consequently, the current dependence on the cultivation of Papaver somniferum is a risk factor that could lead to supply disruptions for morphine and diamorphine. The available product on the global market is subject to yearly fluctuations, for example, due to heavy rains or droughts (42). Additionally, the overall demand for opioids is increasing because developing nations require appropriate amounts of opioids to treat pain. For example, in Uganda, opioid analgesic consumption increased by 342% from 2000 to 2015 but overall remained extremely low (43). This leads to more competition on the global market for poppy straw, which can increase prices if the demand is not met with adequate supply (44, 45).

HOW IS THE MARKET FOR DIAMORPHINE STRUCTURED?

Over the past 20 years, according to the INCB, the licit manufacture of diamorphine worldwide averaged 700 kg annually (32). In 2019, Switzerland manufactured, consumed, and kept the largest stock of diamorphine worldwide (46).

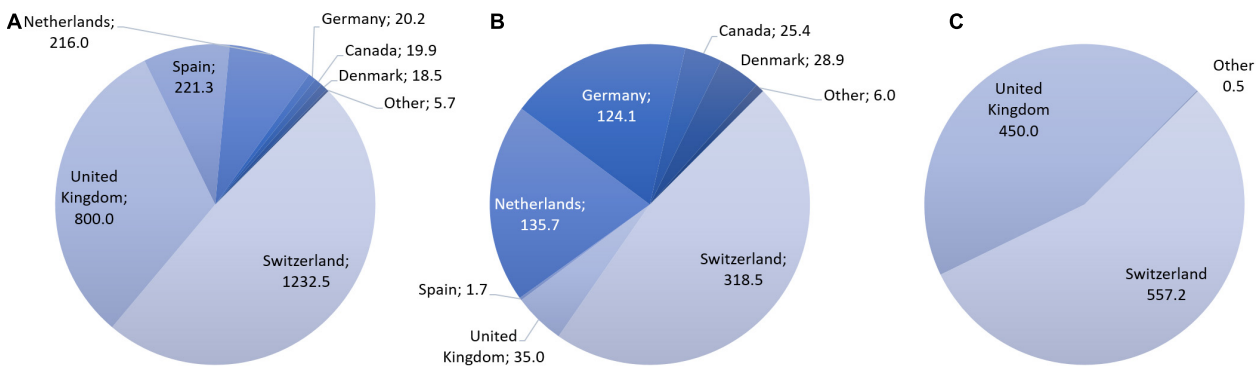

FIGURE 2 | Stocks **(A)**, consumption **(B)**, and manufacture **(C)** of diamorphine in kg per country, 2019. Based on data requested from INCB.

Figure 2C shows that in 2019, a total of 1 metric ton of diamorphine was manufactured by Switzerland and the United Kingdom (557.2 kg, or 55.3%; respectively 450 kg, or 44.7%). Both countries also have the largest stocks of diamorphine in 2019 (Switzerland: 1.2 metric tons; UK 0.8 metric tons), together holding 80.2% of the stocks worldwide (**Figure 2A**).

In 2019, Switzerland accounted for roughly half (318.5 kg, 47.2%) of the global medical diamorphine consumption (675.4 kg). Other countries with significant diamorphine consumption are the Netherlands, Germany, the United Kingdom, Denmark, and Canada (**Figure 2B**). **Table 1** shows that Switzerland's consumption of diamorphine is extraordinarily high when related to its population size compared with the other countries.

Diaphin, is the only authorized diamorphine product in Switzerland, Germany, and Denmark, representing more than two-thirds of the world's diamorphine consumption (3, 47, 48). Hence, DiaMo holds the monopoly in the cited countries and dominates the world market.

ARE THERE LEGAL OR REGULATORY CONSTRAINTS PREVENTING THE INTRODUCTION OF A DIAMORPHINE GENERIC IN SWITZERLAND?

Generally, the first constraint for a generic is the existence of a patent. A patent is an intellectual property right for a technical invention, such as a medicine. It allows its owner to prevent others from using the patented invention for commercial purposes for up to 20 years from the patent application (49, 50). In the case of diamorphine, there were no patents on the substance itself. Indeed, Bayer, who started commercial production of diamorphine, could not patent the substance because it was not new, as the English chemist Charles Wright had already synthesized and published a description of diamorphine in 1874 (51).

Another mechanism is document protection, also called marketing exclusivity; it prohibits competitors from relying upon and referring to data submitted to the authority by the originator company. The Swiss Therapeutic Products Act (TPA) allows 10 years of document protection for new medicines (52, 53). Before the expiry of this period, Swissmedic cannot grant a third party a marketing authorization (typically a generic authorization), which relies on the protected data (54). Swissmedic first approved the 10 g i.v. diamorphine formulation in December 2001 (3). Hence, document protection has long run out. More recently, the originator received document protection for a 5 g i.v. formulation, which will last 3 years, until 29.07.2024 (3, 55). However, this should not discourage potential competitors as the document protection only protects the 5 g formulation. Similarly, even though Diaphin has orphan drug status, it was not granted increased document protection of 15 years because it was registered before 2019 (56, 57).

Another administrative hurdle faced by companies wanting to supply diamorphine in Switzerland is applying for a narcotics license from Swissmedic. However, no exceptional license from the Federal Office of Public Health (FOPH) is needed because diamorphine is the active ingredient of an authorized medicinal product (58, 59). Swissmedic will license persons and companies, including brokers, agents, and the army pharmacy, to handle authorized medicinal products containing schedule d substances, such as diamorphine (60). In practice, it considers companies with a license to handle schedule a substances, e.g., morphine, to be also authorize to handle medicinal products containing schedule d substances (i.e., diamorphine) (61). Indeed, 321 companies had a schedule a narcotic license as of mid-December 2021 (62). All of which would, in theory, be allowed to handle diamorphine.

In summary, there is no patent protection on diamorphine, and document protection only covers 5 g Diaphin i.v. Furthermore, we find that diamorphine is subject to constraints similar to substances such as morphine. Hence, in our opinion, there are no regulatory hurdles that should discourage potential competitors from entering the Swiss market.

HOW DID SWITZERLAND ADDRESS THE 2021 SUPPLY DISRUPTION?

According to a report on the Swiss TDP, the following actions were taken to mitigate the 2021 shortage: allocation by the manufacturer based on past orders and limitation of purchases; recommendation to switch to Diaphin IR or SR tablets or other OAT; and the postponement of the study on the nasal application of Diaphin i.v. (10). The report also stated that a new manufacturer for Diaphin i.v. had been found in the Netherlands, which resolved the 2021 supply disruption (10).

Compulsory stockpiling is a precautionary measure of import-dependent Switzerland; the stocks can be released as needed when the demand for important basic supplies, including medicines, can no longer be met on the market due to a (temporary) shortage. However, diamorphine is not subject to compulsory stockpiling by the marketing authorization holder,

TABLE 1 | Diamorphine consumption and population size of Switzerland, Netherlands, Germany, United Kingdom (UK), Denmark, and Canada in 2019.

Country	Switzerland	Netherlands	Germany	UK	Denmark	Canada
Diamorphine consumption [in kg]*	318.5	135.7	124.1	35	28.9	25.4
% of worldwide consumption	47.2%	20.1%	18.4%	5.2%	4.3%	3.8%
Population [in Mio.]**	8.6	17.3	83.1	66.8	5.8	37.6

**INCB data 2019 **Population data from the World Bank for 2019. https://data.worldbank.org/indicator/SP.POP.TOTL (accessed on 12. January 2021).*

unlike many other opioid medicines such as morphine, fentanyl, and methadone (63). Hence, there were no compulsory stocks that could be released in response to the 2021 supply disruption.

Even though Switzerland seems to have overcome the 2021 supply disruption unscathed, it remains unprepared for a diamorphine shortage.

Compared to Switzerland, the UK has taken a more active approach to managing the risks of a potential diamorphine shortage. In 2006, the UK Office of Fair Trading issued a review that alerted the government of a monopoly situation in the UK (64). The report states: "the Government recognizes that a lack of competition may continue to have a knock-on effect on both downstream prices and the ability of competitors to enter into the market." Nowadays, the UK has several suppliers for diamorphine (**Supplementary Table 1**) but still encounters shortages (65, 66). For example, the 5 and 10 mg diamorphine i.v. formulation has intermittently been in short supply since 2018 despite having two suppliers (66). In response to the supply issues, the UK National Health Service (NHS) issued recommendations and implemented medical guidelines to tackle the shortages (67). The NHS recommended switching patients permanently to morphine sulfate solution, where clinically applicable. Primary and secondary care were asked to ensure that no new patients would be started on the diamorphine i.v. strengths with unstable supply; furthermore, patients patients should not be switched to higher strengths, as there were insufficient stocks to support the increased use.

WHAT DO WE RECOMMEND?

Based on the information we gathered, authorities in Switzerland have done little to address the diamorphine monopoly and potential shortages. Probably because even though shortages loomed, a rupture of stock never occurred. However, the recent supply chain disruption of diamorphine and the shortage of Sevre-Long (slow-release morphine used in OAT) highlight the importance of preparing for a shortage situation (68, 69). Hence, we recommend several actions to prepare for a potential shortage, sorted by the ease of implementation.

First, authorities and relevant stakeholders should elaborate a plan describing actions to take in a shortage situation. The plan should include a national distribution key to attribute the remaining limited stocks of diamorphine among persons in TDP. This medical-ethical (triage) guideline will help physicians to navigate the shortage. Similar to the SARS-COV2 intensive care triage guidelines, there should be a national ethical, systematic and evidence-based framework to approach the patient allocation of scarce medications in general.

Secondly, diamorphine should be added to the list of compulsory stocked medicines to stabilize the supply. Considering that diamorphine has a long shelf life, this preventive measure could help alleviate short-term ruptures in the supply chain of up to 3 months.

Thirdly, long-term options to reinforce the supply chain of diamorphine should be evaluated. Indeed, the report on the Swiss TDP listed four proposals to reinforce the supply chain: optimization of the current supply by the pharmaceutical industry; decentralized manufacturing by hospital pharmacies; procurement through government; and manufacturing by the government (10).

In our view, these proposed measures are not enough to improve the situation long-term, at least as long as the monopoly remains. Decentralized manufacturing by hospital pharmacies carries logistical issues, especially for TDP centers not in close proximity to hospitals, and would likely not be cheap. Procurement by the government through a tender would likely alleviate some of the risks; however, to be successful there must be interested pharmaceutical companies. Alternatively, Switzerland could evaluate other suppliers, for example, from the UK (**Supplementary Table 1**). However, this would be problematic even short-term, because Swiss demand would likely extend beyond the available UK supply, as Switzerland uses almost 10 times more diamorphine annually.

Given the perceived "unattractiveness" of manufacturing diamorphine and the current monopoly, manufacturing by the Swiss army pharmacy should be evaluated. The army pharmacy is the only federal administrative unit in Switzerland that holds Swissmedic licenses to manufacture, import, wholesale trade, and export medicinal products (11). Manufacturing of diamorphine by the army pharmacy is the most radical intervention. It would require allowing the Swiss army pharmacy to compete with the pharmaceutical industry, which is unlikely to gather the needed political support (70).

Lastly, injectable hydromorphone should be evaluated as an alternative to diamorphine. The Canadian NAOMI study, a double-blind study with injectable hydromorphone and diamorphine, demonstrated that patients were unable to detect which one they received (71). The authors stated: "the fact that most patients in the hydromorphone group thought they were receiving heroin suggests that hydromorphone can effectively treat and retain opioid-dependent individuals" (71). The SALOME study provided evidence that the injectable hydromorphone was non-inferior to diamorphine for long-term opioid use disorders (72). Nevertheless, it should be kept in mind that the TDP population often has other psychiatric comorbidities (73, 74), including severe chronic anxiety, which can make them more vulnerable to changes. Hence, switching patients from diamorphine to hydromorphone, in case of a shortage, could destabilize a person in treatment. Moreover, reimbursement could be problematic as hydromorphone would be used off-label, and the treatment with hydromorphone instead of diamorphine would be likely several times more expensive. To our knowledge, there has been no large-scale use of hydromorphone for the treatment of opioid use disorders in Switzerland.

In summary, diamorphine should be added to the list of compulsory stocks, and triage guidelines should be elaborated for the allocation of scarce medicines. The potential of the Swiss army pharmacy to manufacture diamorphine should be evaluated if there are not enough pharmaceutical companies interested in bringing other diamorphine products on the market.

CONCLUSION

In conclusion, Switzerland has so far been lucky in that it has not suffered a shortage of diamorphine; nevertheless, the unstable supply was evidenced recently by reports in Switzerland and Germany. Measures that prevent a shortage in the future and precise planning for a shortage situation must be implemented. TDP is a valuable and successful public health program, and an insufficient supply of diamorphine would affect persons in treatment but also the society as a whole. Switzerland surely does not want to go back to the extreme and very public desperation of the open drug scenes.

DATA AVAILABILITY STATEMENT

The dataset of diamorphine manufacturing, stocks, and consumption in 2019, used in this article, can be requested from the International Narcotics Control Board (INCB). Further enquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CS-K: investigation, data curation, and writing—original draft preparation. CS-K, C-AB, VJ, and OS: writing—review and editing. VJ and OS: supervision and project administration. VJ, C-AB, and OS: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.882299/full#supplementary-material

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MINI REVIEW
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Targeting the Salience Network: A Mini-Review on a Novel Neuromodulation Approach for Treating Alcohol Use Disorder

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Alcohol use disorder (AUD) continues to be challenging to treat despite the best available interventions, with two-thirds of individuals going on to relapse by 1 year after treatment. Recent advances in the brain-based conceptual framework of addiction have allowed the field to pivot into a neuromodulation approach to intervention for these devastative disorders. Small trials of repetitive transcranial magnetic stimulation (rTMS) have used protocols developed for other psychiatric conditions and applied them to those with addiction with modest efficacy. Recent evidence suggests that a TMS approach focused on modulating the salience network (SN), a circuit at the crossroads of large-scale networks associated with AUD, may be a fruitful therapeutic strategy. The anterior insula or dorsal anterior cingulate cortex may be particularly effective stimulation sites given emerging evidence of their roles in processes associated with relapse.

Keywords: alcohol use disorder, neuromodulation, transcranial magnetic stimulation, treatment, salience network, neurocircuitry

INTRODUCTION

Alcohol use disorder (AUD) is the most prevalent substance use disorder (1), imposes the greatest burden of illness (2), and alcohol-induced deaths in the United States are currently on the rise (3). AUD is associated with poor medical, psychological, and social outcomes, such as adverse overall physical health, neuropsychological deficits, psychiatric comorbidities, homelessness, unemployment, and relationship dysfunction (4–6), which contribute to a subsequent poor quality of life for individuals suffering from this devastative disorder. The estimated costs to the American economy were $223.5 billion in 2006 for excessive alcohol drinking (7). Current evidence-based interventions, be it psychotherapy or pharmacological, still result in approximately two-thirds of individuals relapsing by 6-months post-treatment (8). Emerging research into the key brain-based factors that contribute to relapse may reveal novel targets for prediction, intervention, and relapse prevention. To this end, we aim to briefly review the neurocircuitry of addiction, the role of the salience network (SN) in treatment outcomes, the latest trends in neuromodulation for psychiatric disorders, and conclude with a potential avenue for advancing brain-based interventions for AUD.

FUNDAMENTAL CONCEPTUALIZATION OF ADDICTION: A BRAIN-BASED CONDITION

Neurocircuitry of Addiction

Converging lines of evidence from preclinical and human research have resulted in the empirically driven, brain-based conceptual framework of addiction. Animal and human models of addiction have allowed for a sophisticated interrogation of the neurocircuitry that underlies addictive behaviors. Koob and colleagues describe the dynamic allostatic process of the addiction cycle in three stages: (1) binge and intoxication, (2) withdrawal and negative affect, and (3) preoccupation and anticipation stage (9, 10). During the binge and intoxication stages, the reward system is initially hyperactive, specifically the ventral tegmentum and the nucleus accumbens, and following chronic alcohol use, a homeostatic shift to hypoactivation occurs. During withdrawal and negative affect, there is a focus on reduced experiences of reward for conventional stimuli and increases in negative affect. These psychological experiences are coupled with changes in the striatum, extended amygdala, and insula functioning. Finally, the third stage is influenced by stress, increased disinhibition, and leads to preoccupation and anticipation of reward, including craving, which increases relapse risk (11, 12). A core part of this model is the shift from impulsivity fueling early stages of addiction to compulsivity fueling later stages of addiction (including relapse). This co-occurs with a shift from positive reinforcement mechanisms to negative reinforcement mechanisms, which can drive motivated behaviors. At the crossroads of this transition is the SN (13).

The Salience Network

The SN is a multifunctional, intrinsically connected, large-scale neural circuit implicated in several psychiatric conditions, such as addiction. Specifically, the SN is associated with the detection of salient changes in the environment, both interoceptive and external, and signals the need for cognitive control (14). Critical cortical nodes of the SN include the anterior insula (AIns) and the dorsal anterior cingulate cortex (dACC) (14–16). Additionally, these core nodes functionally connect with subregions of the prefrontal cortex (PFC) inferior parietal lobule (IPL) (14, 16–18) and downstream, subcortical regions of the extended amygdala, ventral striatum, and substantia nigra/ventral tegmental area (19, 20). Although intrinsic connectivity of the SN is most often reported during states of rest in humans, SN function is also interrogated during active tasks involving cognition, action, and emotion (19).

Recent work confirms these SN nodes are paralleled in preclinical models (21). In humans, the AIns, dACC, and dorsolateral PFC (dlPFC) co-activate in response to tasks of cognitive demand, cognitive control, decision-making, and environmental uncertainty. This co-activation has previously been implicated in negative mood states (17, 22–24), and synchronous activation has been shown to increase with task difficulty and stimulus ambiguity. This finding, of task difficulty-dependent, increased activation, suggests that the dACC and AIns both play an integral role in cognition by filtering and integrating internal and external stimuli during a variety of cognitive tasks (25).

The insular cortex is involved in various cognitive and affective processes, such as responding to internal and external emotionally salient stimuli, decision-making, threat recognition, and conscious urges (26). The insula is also heavily implicated in interoception, which involves integrating a wide array of somatic physiological conditions to maintain homeostasis (27, 28). The role of the AIns in the SN includes bottom-up detection of salient stimuli *via* integration across perceptual modalities (29–33). Specifically, the AIns plays a key role in externally orienting attention and internally orienting self-related cognitions through engagement with default mode and executive networks (14, 34–37).

Conversely, the dACC plays a crucial role in initiation, motivation, and goal-directed behaviors (38–41), with key projections that influence motor responses (42–44) and interactions with other large-scale networks that have a major role in motor/behavioral selection (25). In addition to co-activation with separate functional networks, the dACC also possesses extensive cortico-cortical connections within the PFC, including the dorsolateral prefrontal cortex (dlPFC) and premotor regions, making it critical for learning and behavior (45). Taken together, the fundamental nodes of the SN—the AIns and dACC—are implicated in the processing and synthesis of several complex human experiences, such as cognition, action, and emotion (19). These critical functions are central to the development and maintenance of addiction (10).

SN in AUD: Intersection With Neurocircuitry of Addiction

Regardless of clinical phenotype, the AIns and dACC are consistently implicated in the development and persistence of multiple psychiatric disorders, such as addictive disorders, suggesting they are critical for psychological well-being and adaptive functioning (46–48). For addiction specifically, the SN may interact and influence incentive salience (49, 50), negative affect (51–55), and executive function (56–60) networks, which are core neurocircuitry underlying AUD (61, 62). The Competing Neurobehavioral Decision System theory, alongside the Impaired Response Inhibition and Salience Attribution models, among others, are established conceptual frameworks of addiction that unite both behavioral and neurobiological systems involved in AUD (63). These models specify that the cortico-striatal circuits involved in processing salient internal or external stimuli, as well as cognitive decision-making, are compromised in AUD. Preclinical literature has identified regions, such as the dACC, insula, and striatum, as targets that are causally linked to alcohol-seeking behaviors (64). In humans, SN abnormalities contribute to difficulties with impulsivity, compulsivity, and executive dysfunction (65, 66), and an increased relapse risk in AUD (4).

The first study to suggest the AIns may have a critical role in the addiction cycle was by Naqvi et al. (67), showing that structural damage to the insula disrupted cigarette consumption. Following a right or left insula lesion, individuals demonstrated

rapid and extended smoking cessation, had fewer conscious smoking urges during abstinence (67), and were five times more likely to quit smoking compared with people with no insula lesion (68). Structural damage to the insula has also been shown to decrease the occurrence and severity of nicotine withdrawal symptoms (69), and smoking cessation difficulty (68). Taken together, these fundamental lesion studies highlight the role of the insula in withdrawal and relapse.

Dysfunction of the dACC has also been intensively described as having a role in psychiatric conditions, such as the development and maintenance of AUD. For example, prior studies have demonstrated that reduced dACC activation and compromised connectivity of the SN nodes are associated with greater decision-making latency in AUD (70, 71). Similarly, in individuals who reported binge drinking, acute alcohol consumption caused blunted functional connectivity between the bilateral AIns and the ACC (72). Several groups have demonstrated that such neurobiological abnormalities of the SN are related to the inability to restrain subjective urges (71) and evaluate emotionally salient stimuli (72) in AUD, further supporting that dysregulation of the SN in AUD (63), across resting state, social and emotional processing, and inhibitory control tasks, such as specific reductions in blood flow (73). Acute alcohol consumption significantly attenuates bilateral anterior insula activation to emotional face cues relative to neutral faces and is exacerbated by the level of response to alcohol, which increases the risk for AUD development (74, 75). SN dysfunction, such as structural and metabolic abnormalities (4, 5, 76) and reduced functional connectivity among nodes of the SN, is also predictive of future relapse in AUD (77, 78).

Similar evidence also points to the insula and the dACC playing major roles in reactivity to alcohol cues. A systematic review of over 100 task-related imaging studies by Zilverstand et al. revealed hyper-activation and hyper-connectivity during substance cue exposure, but blunted activation and reduced connectivity during all other tasks, such as cognitive control, non-substance reward, and social/emotional tasks (63). Other cue reactivity studies have found that neural activation in the insular cortex and the ventral striatum can be used to differentiate between heavy and light alcohol drinkers, with heavy drinkers having a higher activation in those regions in response to alcohol cues (79). This differentiation of neural activation between levels of alcohol use may also provide insights into who is at the highest risk of relapse (26). For example, Kohno and colleagues reported that individuals who did not complete AUD treatment showed increased resting-state connectivity between the striatum and the insula, demonstrating that SN dysfunction could be predictive of future drinking (77).

In summary, evidence suggests that insula and dACC activation and connectivity to other key nodes of the SN and how they relate to the neurocircuitry of addiction are highly relevant to the development and maintenance of AUD. One approach to improving treatment outcomes for these individuals may be to directly target SN function through novel therapeutic techniques that have demonstrated efficacy in other psychiatric conditions.

RESEARCH GAPS: ADVANCING TREATMENT FOR AUD

Among the different treatment options available for AUD, inpatient detoxification for alcohol appears to be the most frequently utilized (80). Residential treatment programs typically apply pharmacotherapies and/or behavioral interventions, such as cognitive-behavioral therapy, group-based peer support, and relapse prevention strategies. However, even with extensive, residential treatment, relapse rates remain high. One potential limitation of existing interventions is that they modify behaviors globally with indirect effects on the brain. Non-invasive neuromodulation techniques demonstrate promise by modifying specific and selective neural targets shown to be associated with symptoms. The current modest efficacy of evidence-based interventions, combined with increasing rates of alcohol-related deaths, makes the development of new brain-based therapeutics a high priority.

Transcranial magnetic stimulation (TMS) is a brain modulation technique that involves the use of different frequencies and patterns of stimulation to generate an electromagnetic field to depolarize neurons and influence cortical excitability. Apart from having FDA clearance for treatment, several resources describe guidelines for treatment and safety protocols (81–86). Extensive research supports the clinical efficacy of TMS for psychiatric disorders, most commonly for major depressive disorder (MDD), after FDA approval in 2008 (81). Since 2008, TMS has received FDA clearance for the obsessive-compulsive disorder (OCD) and smoking cessation (87, 88). Researchers have aimed to expand TMS indications for comorbidities associated with MDD, such as OCD, bipolar disorder, PTSD, and substance use disorder (83, 84). Additionally, researchers have tested altering the standard treatment protocol (89) or using high-efficiency forms of TMS, such as intermittent Theta Burst Stimulation (iTBS) (90) in hopes of increasing efficacy and/or decreasing overall treatment time.

To date, treatment approaches for TMS in AUD have predominately targeted two brain regions: the dlPFC, and the medial prefrontal cortex (mPFC). While meta-analytic studies are difficult to utilize given the inconsistency in the treatment parameters used (e.g., as shown in Ref. (91), a few brief trends have emerged: (1) 10 Hz left or right-sided, dlPFC protocol for the treatment of AUDs is generally helpful in reducing craving (92, 93); (2) the right-sided dlPFC has variable results which may or may not be related to the frequency at which treatment is delivered (92, 94); (3) mPFC stimulation consistently reduce brain reactivity to alcohol cues (95–97), and may reduce alcohol use post-treatment (98, 99); and (4) regardless of stimulation site and chosen TMS parameters, applying 10+ sessions of TMS appears to consistently decrease alcohol craving (94, 98, 100, 101). While results are promising, it is notable that many of these studies focus on craving and have not directly reduced alcohol consumption or relapse risk (92, 94–97, 100–106). While the mixed results within the field may be due to differences in parameter application (frequency, strength of stimulation, and

TABLE 1 | Summary of all transcranial magnetic stimulation (TMS) studies in alcohol use disorder (AUD) to date.

Ref	N (Active, Sham)	rTMS parameters					Outcome measure				Findings	Blind	Active sham control
		Site	Hz	%MT	Sessions; Duration	Pulses/ Session	Drinking Behavior	Craving	Brain/ Biology	Other Bx			
Mishra et al. (93)	45 (30,15)	R.dlPFC	10	110	10 1 month	1,000	1-mo relapse	ACQ-NOW	N/A	N/A	↓ in craving; relapse 14% active, 33% sham	S	Y
De Ridder et al. (115)	1	dACC	1	50	1 1 day	600	N/A	VAS	BOLD	N/A	↓ in craving ↓ BOLD in dACC and PCC	N/A	N/A
Höppner et al. (102)	19 (10,9)	L.dlPFC	20	90	10 10 days	10,000	N/A	OCDS	N/A	AB	No diff in craving/dep sx ↑ in AB effect to alc-stim	S	N
Herremans et al. (103)	31 (15,16)	R.dlPFC	20	110	1 1 day	1,560	N/A	OCDS	N/A	N/A	No diff in craving	S	N
Herremans et al. (104)	29 (29,29)	R.dlPFC	20	110	1 2 days	1,560	N/A	OCDS	N/A	Go-NoGo	No difference in craving ↓ IIRTV of Go-NoGo	S	N
Ceccanti et al. (99)	18 (9,9)	dmPFC	20	120	10 10 days	1,000	TLFB	VAS	cortisolemia, prolactinemia	N/A	↓ craving ↓ # drinks per day/max ↓ cortisol and prolactin	D	Y
Girardi et al. (100)	10	L.dlPFC	20	120	20 1 month	2,200	N/A	OCDS	N/A	N/A	↓ craving/depressive sx	N/A	N/A
Herremans et al. (94)	26 (13,13)	R.dlPFC	20	110	15 4 days	1,560	N/A	AUQ, OCDS	BOLD	N/A	↓ craving, not cue-induced ↑ reward ↓ DMN BOLD	N/A	N/A
Jansen et al. (105)	38 (20,18)	R.dlPFC	10	110	1 1 day	3,000	N/A	VAS	FC	N/A	↑ fcMRI of frontal pole	S	N
Mishra et al. (92)	20 (10 L, 10 R)	L.dlPFC R.dlPFC	10	110	10 10 days	1,000	N/A	ACQ	N/A	N/A	↓ in craving both left and right stimulation	D	N/A
Rapinesi et al. (101)	11	L.dlPFC	18	120	20 4 weeks	1,980	N/A	OCDS	N/A	N/A	↓ in craving/dep sx sustained at 6-months	N/A	N/A
Herremans et al. (116)	19	R.dlPFC	20	110	14 3 days	1,560	1-mo relapse	N/A	BOLD	N/A	68% relapse at 1mo ↓ dACC BOLD abstainers ↑ dACC BOLD relapsers	S	N
Qiao et al. (106)	38 (18,20)	R.dlPFC	10	80	4 5 days	800	N/A	N/A	MRS	HVLT, BVMT	↑ memory ↑ NAA/Cr and Cho/Cr	D	N
Del Felice et al. (117)	17 (8,9)	L.dlPFC	10	100	4 2 weeks	1,000	N/A	VAS	EEG	Stroop, Go-NoGo	No change in craving ↑ Stroop/Go-NoGo ↓ EEG/dep sx	S	N
Addolorato et al. (118)	11 (5,6)	L.dlPFC R.dlPFC	10	100	12 4 weeks	1,000	TLFB	OCDS	SPECTDAT	N/A	No diff in craving/dep sx ↓ in STAI-Y, DAT ↑ # of abstinent days,	D	Y
Hanlon et al. (95)	50 (25 coc, 25 alc)	vmPFC	5	110	6 1 day	3,600	N/A	N/A	BOLD	N/A	Alcohol: ↓ BOLD mPFC, AIns, MTG, and parahippocampal gyrus	S	Y
Hanlon et al. (96)	49 (25 coc, 24 alc)	vmPFC	5	110	6 1 day	3,600	N/A	VAS	BOLD	N/A	Alcohol: ↓ BOLD OFC, insula, and lateral sensorimotor cortex	S	Y
Kearney-Ramos et al. (97)	49 (25 coc, 24 alc)	vmPFC	5	110	6 1 day	3,600	N/A	VAS	FC	N/A	Alcohol: No diff in craving ↓ cue-related fcMRI of reward regions	S	Y
McNeill et al. (119)	20 (w/in-design)	R.dlPFC	50	80	1 1 day	600	drinking	N/A	N/A	Stop-signal	↓ inhibitory control ↑ alcohol consumption	N/A	N
Wu et al. (120)	51 (22, 29)	R.dlPFC	20	110	153 days	1,560	1-mo relapse	N/A	GMV	N/A	↓ GMV in relapsers, No change in TMS GMV but baseline predicted relapse	N/A	N/A
Perini et al. (121)	56 (29,27)	Bi-Insula	10	120	15 3 weeks	1,500	No TLFB	AUQ, PACS	BOLD	N/A	No diff in craving, drinking measures, fMRI	D	Y
Harel et al. (98)	51	mPFC ACC	10	100	15 3 weeks 5: 3mo fu	3,000	TLFB	PACS	FC	AUDIT ADS	↓ craving, ↓ % heavy drinking ↓rsFC dACC to caudate nucleus ↓FC mPFC to subgenual ACC.	D	Y

Search terms included: alcohol use disorder and transcranial magnetic stimulation between 2010 and 2021. A review of the resulting articles was conducted by CBP and excluded position papers and reviews.

number of sessions), another limitation may be that protocols were only able to stimulate the outermost cortex, rather than deeper nodes within the SN.

Recent technological advances in TMS coil design have made it possible for TMS-induced electric fields to penetrate deeper into the brain, modulating areas, such as the dACC and AIns in addition to superficial cortical areas (107). Recent studies indicate that these newly developed H-coils tend to provide both a broader area of stimulation and increased depth as compared with the Figure-of-8 coil [see Tendler et al. (107) for a review of the various H-coil designs and exact cortical targets]. Furthermore, the design of the H-coils can provide simultaneous activation of both the left and right lateral and medial prefrontal cortices depending on the specific coil and the treatment parameters used (107). Although this design stimulates both hemispheres, there is evidence to suggest that it stimulates the left hemisphere more than the right (108, 109). Given that the electromagnetic fields delivered by TMS decay exponentially with distance (110, 111), specific confirmation is needed to determine if these deep TMS devices can stimulate subcortical regions, such as the AIns and the dACC. This is of particular relevance in AUD, wherein alcohol is known to induce widespread cortical atrophy (112). That said, a recent study investigating the distance from the scalp to the cortex at the dlPFC and mPFC among a sample of individuals with AUD and healthy controls did not find a significant difference between the groups (113).

Similar to the mood disorders literature, targeting may be critical in addition to overall dosage (i.e., the total number of pulses administered during a treatment course) when considering how best to achieve downstream network effects (114). **Table 1** summarizes all TMS studies to date in AUD, which clearly emphasizes that the field of targeting subcortical nodes within the SN is in its infancy. Among the sparse, existing literature, evidence suggests that cue-induced craving may be better modulated by targeting inferior structures, such as the ACC, the insula, or the mPFC (99, 122). However, the literature on how to best modulate insular and cingulate activity also provides disparate information. Results from Perini et al. suggest that insular stimulation made no difference in resting-state connectivity or craving in treatment vs. sham groups (121) for AUD. These results are particularly important to consider given the involvement of the insula in AUD circuitry (26). Harel and colleagues recently reported that an H7 stimulation protocol targeting the dACC resulted in changes in functional connectivity *and* fewer heavy drinking days in the active condition compared with the sham condition (98). While these early works have produced mixed results, the converging preclinical and clinical evidence regarding the centrality of SN nodes in the development and maintenance of AUD warrants further investigation.

Other Considerations Moving Forward

As described above, the SN nodes are likely promising brain-based targets for therapeutic intervention, particularly by utilizing unique forms of TMS as tools to modulate deeper brain structures. However, one of the constraints of TMS is that current technology cannot reach the insula or dACC without also delivering a strong electric field to the superficial cortical areas between the TMS coil and the deeper brain target (as shown in **Figure 1**). To move the field forward, it is important to think creatively about non-invasive brain stimulation options that may allow us to selectively activate core SN nodes without simultaneously activating off-target cortical regions.

There are several complementary non-invasive approaches that may be useful for the field to consider as it evaluates the SN as a fruitful target for AUD treatment. One possibility

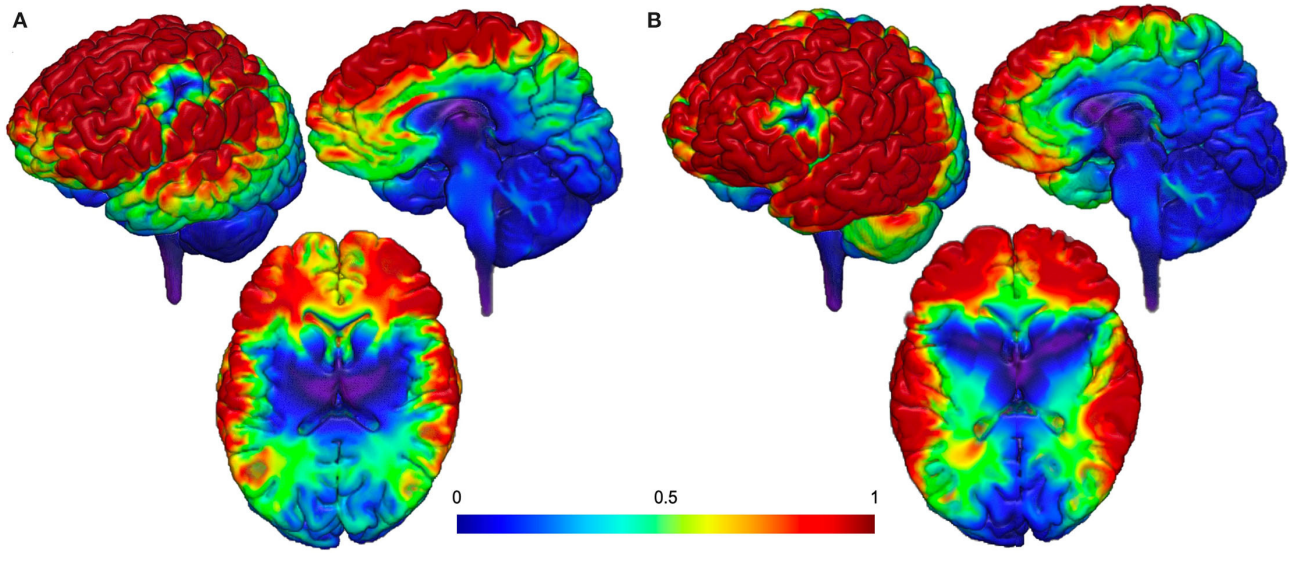

FIGURE 1 | Proposed theoretical electrical field models (113). **(A)** Targeting dACC stimulation and **(B)** targeting AIns stimulation. Both models demonstrate additional delivery of a strong electrical field to the superficial cortical areas between the TMS coil and the deeper brain target.

is to use temporally interfering electric fields non-invasively applied at multiple cortical locations simultaneously. Grossman and colleagues recently demonstrated that by exploiting the inherent sensitivity of neural populations to varying frequencies, it is possible to selectively stimulate the mouse hippocampus. It remains unclear if this would yield similar results in humans.

Finally, while our focus has been on deep TMS (dTMS) potential, it is also possible to modulate these brain regions through a targeted cortical area with strong afferent projections to the cingulate or insula. This "cortical window" approach relies on the known ability of TMS to modulate areas monosynaptically connected to the area targeted by the electric field. This simple principle is evident by the basic generation of a motor evoked potential in the hand following stimulation of the primary motor cortex (a 2-synapse network). For example, active TMS applied to the frontal pole can change functional connectivity with the insula and cingulate cortex, when compared with sham TMS (96, 97). These are just a few considerations that the field may find fruitful when searching for a strategy to non-invasively modulate the SN nodes.

CONCLUSION/DISCUSSION: POTENTIAL DEVELOPMENTS FOR THE FIELD

Alcohol use disorder is highly prevalent, devastating, and notoriously difficult to effectively treat, as evidenced by the nearly two-thirds relapse rate within 6 months of treatment (123–125). One potential limitation of existing psychosocial and pharmaceutical interventions is that they modify behaviors more globally with indirect effects on the brain. Non-invasive neuromodulation techniques are showing promise toward the aim of modifying specific and selective neural targets related to AUD. However, device-based interventions to date for AUD have focused on superficial cortical stimulation, with most outcomes being related to craving. In contrast, preclinical and clinical studies suggest that deeper nodes within the SN could be promising targets, particularly the AIns and the dACC. Deep rTMS (dTMS) is one type of neuromodulation technique, utilizing an H-coil design (currently FDA-cleared for OCD and smoking cessation) that can potentially reach the AIns and dACC (126). However, it remains unclear if these targets are modifiable in AUD and which SN node (AIns or dACC or both) would have a greater impact on SN function, and importantly on reducing relapse risk post-treatment. Several lines of evidence support the SN as a promising future target for neuromodulation to impact treatment outcomes for AUD, and this warrants further investigation.

AUTHOR CONTRIBUTIONS

CP: conceptualization, resources, writing—original draft, supervision, and funding acquisition. L-TT: writing—original draft and writing—review and editing. DM: writing—review and editing and visualization. HA-D: literature review and writing—review and editing. CH, LW, FK, BK, TD, and JY: writing—review and editing. MM: conceptualization, resources, writing—original draft, and supervision. All authors contributed to the article and approved the submitted version.

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The Counterproductive Effect of Right Anodal/Left Cathodal Transcranial Direct Current Stimulation Over the Dorsolateral Prefrontal Cortex on Impulsivity in Methamphetamine Addicts

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The current study aimed to evaluate the effect of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) on behavioral impulsivity in methamphetamine addicts. Forty-five methamphetamine addicts were recruited and randomly divided into active tDCS and sham tDCS groups to receive a daily tDCS intervention for 5 days, with the intensity set to 2 mA for the active group and 0 mA for the sham group. Anodal and cathodal electrodes were, respectively, placed over the right and left DLPFC. Behavioral impulsivity in methamphetamine addicts was examined by the 2-choice oddball task at 3-time points: before tDCS intervention (baseline), after the first intervention (day 1), and after 5 repeated interventions (day 5). Besides, twenty-four healthy male participants were recruited as the healthy controls who completed a 2-choice oddball task. Analysis of accuracy for the 2-choice oddball task showed that behavioral impulsivity was counterproductively increased in the active group, which was shown by the decreased accuracy for the deviant stimulus. The results suggested that the present protocol may not be optimal and other protocols should be considered for the intervention of methamphetamine addicts in the future.

Keywords: impulsivity, methamphetamine, transcranial direct current stimulation, dorsolateral prefrontal cortex, two-choice oddball

INTRODUCTION

Substance use disorders are prevalent health problems that are accompanied by mental disorders (1) and physical dysfunction (2), even underlying factors in criminal behavior (3). Individuals who chronically use methamphetamine exhibit higher behavioral impulsivity (4) which may result in constant drug use and relapse (5, 6). Behavioral impulsivity or behavioral disinhibition refers to the inability to inhibit a prepotent action (7). Previous studies have found that methamphetamine addicts exhibit higher behavioral impulsivity than healthy controls (8, 9), which persisted about 10 months after methamphetamine addicts abstained naturally (10). Behavioral inhibition is associated with most current therapies for methamphetamine addiction, which treat individuals

by increasing their behavioral inhibition ability (11). Therefore, it is expected that a robust therapy outcome can be obtained by decreasing the behavioral impulsivity of methamphetamine addicts.

Methamphetamine addicts have shown structural (12, 13), metabolic (14), and functional (15) abnormalities in the frontal cortex, such as the dorsolateral prefrontal cortex (DLPFC). The DLPFC plays a primary role in the execution and inhibition of behavior, and its impairment decreased the ability to inhibit behavior (16). Notably, recent evidence suggested that using transcranial direct current stimulation (tDCS) to stimulate the DLPFC decreases behavioral impulsivity in individuals with attention deficit hyperactivity disorder (17), Gambling Disorder (18), and healthy individuals (19). However, it is unclear whether tDCS may effectively decrease behavioral impulsivity in methamphetamine addicts.

Transcranial direct current stimulation is a method of non-invasive brain stimulation, which has been used in the intervention of various psychiatric disorders (20) and the enhancement of cognitive function (21). The protocol of tDCS is crucial to the effectiveness of the technique (22). Previous studies have found a variety of tDCS protocols effective in decreasing craving in methamphetamine addicts (23–25), such as bilateral tDCS over the DLPFC (right anodal/left cathodal). This protocol has been shown to be effective in decreasing the symptoms of addiction, impulsivity in some substance addictions (e.g., tobacco and cocaine), or psychiatric disorders (18, 26, 27). In addition, multi-session of tDCS intervention has been found more effective than one session (28). Therefore, it can be expected that multi-session bilateral tDCS over the DLPFC (right anodal/left cathodal) can effectively decrease impulsivity in methamphetamine addicts.

Based on the evidence above, we hypothesized bilateral tDCS over the DLPFC (right anodal/left cathodal) may decrease behavioral impulsivity in methamphetamine addicts. To test this hypothesis, the current study used a 2-choice oddball task to examine behavioral impulsivity, as it has been shown to be effective in measuring behavioral impulsivity (29). The 2-choice oddball task requires participants to respond to two types of stimuli accurately and then quickly: one is standard and the other is deviant. The ratio of standard to deviant stimuli is 4 to 1, which means participants would be more habitual to respond to the standard stimulus; when a deviant stimulus presents, participants would inhibit their habitual response. Therefore, the accuracy and response time (RT) for deviant stimulus can be served as indicators of behavioral impulsivity (30).

MATERIALS AND METHODS

Participants

According to *a priori* computation of the required sample size in the current design using G*Power statistical software (31), 36 individuals are necessary for 0.95 statistical power, and 45 individuals were used in the current study. The effect size was set to a threshold of medium (i.e., 0.25), according to previous meta-analysis reports regarding the effect of tDCS on drug addiction (28, 32), and the alpha was set to 0.05.

Forty-five individuals with methamphetamine addiction were recruited from Sichuan Ziyang Drug Rehabilitation Center, Sichuan Province, China. They were found by the police when they took drugs for the last time, and then they received unified management and treatment in the drug rehabilitation center, and have no chance to take drugs for 2 years. Inclusion criteria included meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, never using drugs other than methamphetamine, and no acute physical or mental illness. Exclusion criteria included history of multiple drug use, current methamphetamine use or medication, history of acute physical and mental problems (e.g., epilepsy, stroke, cardiovascular disease), presence of metal implants (e.g., electrodes, pacemakers, heart bypass), and history of brain stimulation interventions. Each methamphetamine addict was randomly assigned to an active tDCS group ($n = 23$) with a 2 mA current intensity or a sham tDCS group ($n = 22$) with a 0 mA current intensity, according to a computer-generated randomization sequence. The overall mean age of the methamphetamine addicts was 24.1 (SD = 2.13) years, 24.3 (SD = 1.57) years in the active group, and 24 (SD = 2.62) years in the sham group. Additionally, 24 healthy male participants were recruited as healthy controls. Their mean age was 25.2 (SD = 4.14) years. The three groups were matched in age, $F_{(2,66)} = 1.129$, $p = 0.33$, $\eta_p{}^2 = 0.033$.

All participants were right-handed and had normal or corrected-to-normal vision. They voluntarily participated in the study and signed written informed consent before receiving the intervention. The current study has been registered on the platform of the China Trial Registration Center (Registration number: ChiCTR2100046112) and has been approved by the Ethical Committee of the Institute of Brain and Psychological Sciences, Sichuan Normal University in China. The experimental procedure was in line with principles of the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines; see **Figure 1**.

Transcranial Direct Current Stimulation Procedure

"Direct currents of 2 mA generated by an electrical stimulator (Brain Premier tDCS Device; China) were applied through a pair of saline-soaked 1.5" round sponge electrodes for 20 min. In both active and sham groups, anodal and cathodal electrodes were placed over the right and left DLPFC, respectively (F4-F3), which was determined *via* the standard tDCS navigation system provided by the NeuStim NSS18 equipment of Neuracle Company (Changzhou, China). For the sham group, the direct current intensity is set to 0 mA and the intervention time is the same as the active group. To test the effectiveness of the sham protocol, after the intervention, participants were randomly selected and asked orally about their feelings. The tDCS intervention was performed for 5 sessions over 5 consecutive days. The experimenter who applied tDCS was blind to the study hypothesis but not to the setting of two groups (active vs. sham).

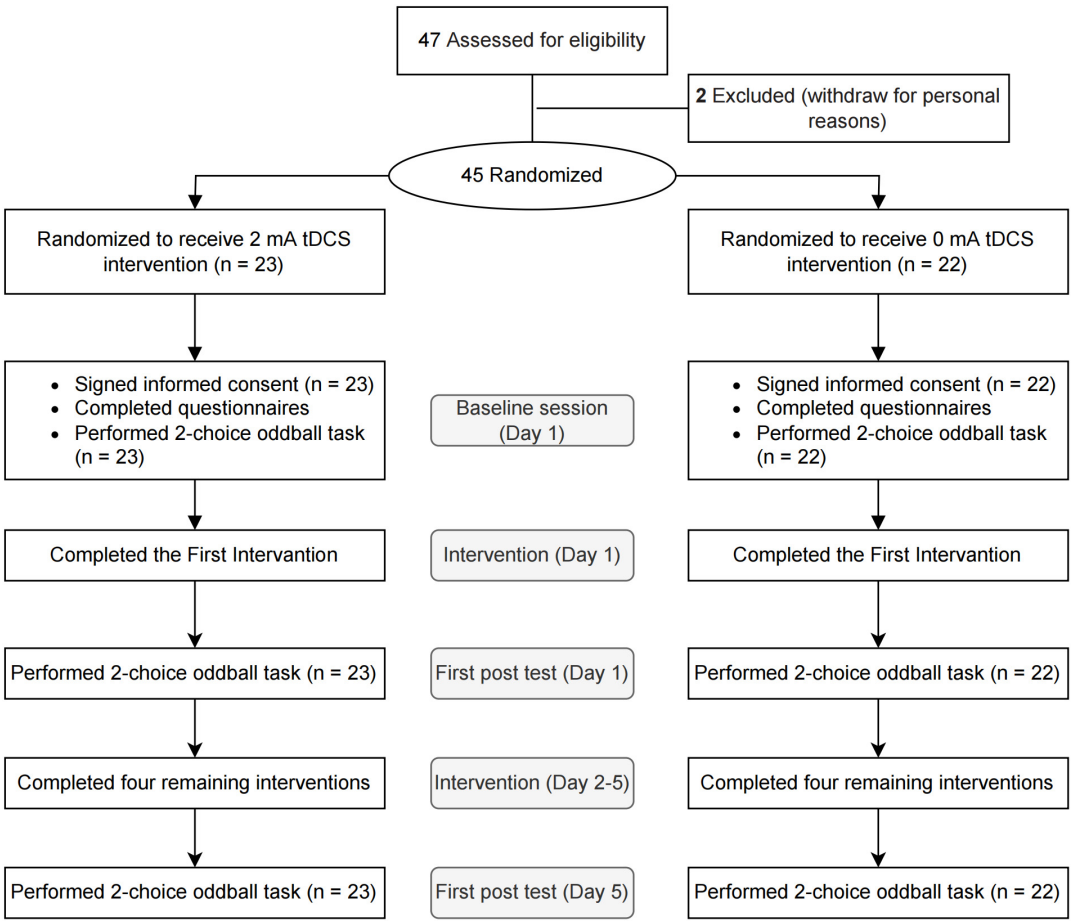

FIGURE 1 | Flow-chart of the experimental procedure.

Behavioral Measurement

The two-choice oddball task contained 200 trials, including 160 standard stimuli ("W") and 40 deviation stimuli ("M"). Each trial started with a jittered fixation cross appearing at the center of the screen and varying from 500 to 1,500 ms. For the participants in each group, if the standard stimulus was presented, they were to press the "F" key with their left index finger as quickly as possible. If the stimulus was deviant, they were to press the "J" key with their right index finger. Before the task started, each participant completed 15 practice trials to familiarize themself with the procedure. To avoid the practice effect, the formal experiment did not start until participants achieved 100% accuracy in both standard and deviant stimuli during practice. At the end of the experiment, the accuracy was given as feedback to participants.

Behavioral impulsivity was primarily indicated by the accuracy of the deviant stimulus. In the methamphetamine addicts group, behavioral impulsivity was examined at 3-time points: before tDCS intervention (baseline), after the first intervention (day 1), and after 5 repeated interventions (day 5). Besides, healthy controls completed a 2-choice oddball task as the baseline impulsivity level of healthy individuals.

Data Analysis

To verify the effectiveness of the manipulation, we collected the RT and accuracy from the 2-choice oddball task and used the baseline data to conduct a 2×2 mixed-design ANOVA, with stimulus (standard, deviant) as within-subject factor and group (healthy controls, methamphetamine addicts) as between-subject factor. To analyze the effect of tDCS on behavioral impulsivity in methamphetamine addicts, a $2 \times 3 \times 2$ mixed-design ANOVA was used, with group (sham, active) as between-subject variable, session (baseline, day 1, day 5), and stimulus (standard, deviant) as within-subject variables. Potential group differences in demographic data and questionnaires were analyzed using independent samples *t*-tests, ANOVA, and Kruskal–Wallis tests, as appropriate.

According to the Greenhouse–Geisser method, the degrees of freedom for *F*-ratios that violate the spherical assumption are corrected. The false discovery rate (FDR) correction was used for *post-hoc* comparisons if statistically significant main or interaction effects appeared. All statistical analyses were performed in R (33). A 2-sided $p < 0.05$ was considered statistically significant, and the effect size was reported as partial η^2 (η_p^2).

RESULTS

The mean abstinence duration was 153 (SD = 78.3) days in the active group, and 123 (SD = 58.6) in the sham group, and the 2 groups were overall matched in the duration of abstinence ($p = 0.15$). The three groups were matched on other demographic variables, demographic data are presented in **Table 1**.

Manipulation Check

Baseline data were used to check the effectiveness of manipulation. The mixed-design ANOVA of accuracy and RT in the 2-choice oddball task showed statistically significant group-by-stimulus interaction effects, accuracy, $F_{(1,67)} = 4.204$, $p = 0.044$, $\eta_p^2 = 0.059$; RT, $F_{(1,67)} = 12.016$, $p < 0.001$, $\eta_p^2 = 0.152$. The deviant stimulus had lower accuracy and longer RT relative to the standard stimulus in both samples ($ps < 0.001$), indicating that the experimental manipulation was effective and that the 2-choice oddball task could successfully measure behavioral impulsivity. Notably, although methamphetamine addicts and healthy controls showed similar accuracy in the standard stimulus ($p = 0.606$) and RT for the deviant stimulus ($p = 0.479$), the accuracy of the deviant stimulus ($p = 0.033$) and the RT for the standard stimulus ($p = 0.003$) was significantly lower in methamphetamine addicts compared with healthy controls, indicating that methamphetamine addicts showed higher behavioral impulsivity relative to healthy controls; see **Figure 2**.

The Effect of Transcranial Direct Current Stimulation on 2-Choice Oddball Task

The mixed-design ANOVA of accuracy showed a statistically significant 3-way interaction among stimulus, session and group, $F_{(1.62,69.51)} = 5.96$, $p = 0.007$, $\eta_p^2 = 0.122$. The simple effects analysis found a significantly decreasing deviant stimulus accuracy ($p < 0.035$) and no significantly different standard stimulus ($p > 0.296$) after 5 days of interventions in the active group. Importantly, this significant stimulus-by-time interaction only found in the active group, $F_{(1.46,32.13)} = 6.354$, $p = 0.009$, $\eta_p^2 = 0.224$, but not in the sham group, $F_{(2,42)} = 0.686$, $p = 0.509$, $\eta_p^2 = 0.032$. These results indicated a significantly increased behavioral impulsivity after 5 consecutive days of interventions in the active group, and no difference in the sham group; see **Figure 3**.

The analysis of RT found no statistically significant three-way interaction among stimulus, time and group, $F_{(2,86)} = 2.826$, $p = 0.065$, $\eta_p^2 = 0.062$, except for a significant stimulus by time interaction, $F_{(2,86)} = 21.876$, $p < 0.001$, $\eta_p^2 = 0.337$, and a significant group by stimulus interaction, $F_{(1,43)} = 6.105$, $p = 0.018$, $\eta_p^2 = 0.124$. Further analysis revealed that, regardless of the active group or the sham group, the RT for the standard stimulus significantly decreased over time (both: $ps < 0.006$), while the RT for the deviant stimulus was not significantly different before and after the interventions (both: $ps > 0.124$).

DISCUSSION

The current study aimed to evaluate the effect of bilateral tDCS (right anodal/left cathodal) over DLPFC in decreasing behavioral impulsivity in methamphetamine addicts. Inconsistent with our hypothesis, the results suggested that the current protocol of bilateral tDCS counterproductively increased impulsivity in methamphetamine addicts. Specifically, after 5 consecutive days of intervention, the accuracy for deviant stimulus was significantly decreased in the active group, while the sham group did not.

Mounting evidence indicated that the DLPFC is closely linked to behavioral control. Previous studies have found that individuals with impaired DLPFC generally performed worse on executive measures relative to healthy individuals and individuals with damage in other brain regions (34). Moreover, some studies have found that stimulating the DLPFC of individuals through tDCS decreased the impulsivity of healthy

TABLE 1 | Demographic data of methamphetamine addicts undergoing active or sham tDCS and healthy controls.

	Methamphetamine addicts				
Characteristic	**tDCS**	**Sham**	**Healthy controls**	F/χ^2	***p*-value**
Sex	Male	Male	Male	NA	NA
Participants, No.	23	22	24	NA	NA
Age, mean (SD), y	24.3 (1.57)	24.0 (2.61)	25.3 (4.14)	1.19	1.31
Education[a]	2.30 (0.82)	1.91 (0.81)	2.38 (0.77)	4.85	0.09
Smoking	2.26 (1.10)	2.41 (1.05)	2.00 (1.06)	0.87	0.43
SAS	29.8 (8.24)	32 (6.87)	31.7 (3.71)	0.88	0.42
SDS	34.0 (5.59)	34.7 (7.17)	35.6 (7.23)	0.4	0.67
BIS	71.4 (14.9)	75.9 (18.6)	70.8 (12.1)	−0.81	0.42
Rehabilitation	153 (78.3)	123 (58.6)	NA	−1.47	0.15
Addiction[b]	2.56 (0.73)	2.5 (0.80)	NA	0.06	0.81

[a] *Unit for Education: denoted as 1 for primary school, educated for 6 years; 2 for junior high school, educated for 9 years; 3 for senior high school, educated for 12 years; 4 for college, educated for 16 years.*

[b] *Unit for Addiction: denoted as 1 for addicted for 2 years and below; 2 for addicted for 3–5 years; 3 for addicted for 6–10 years; 4 for addicted for 11 years and above. NA means not available.*

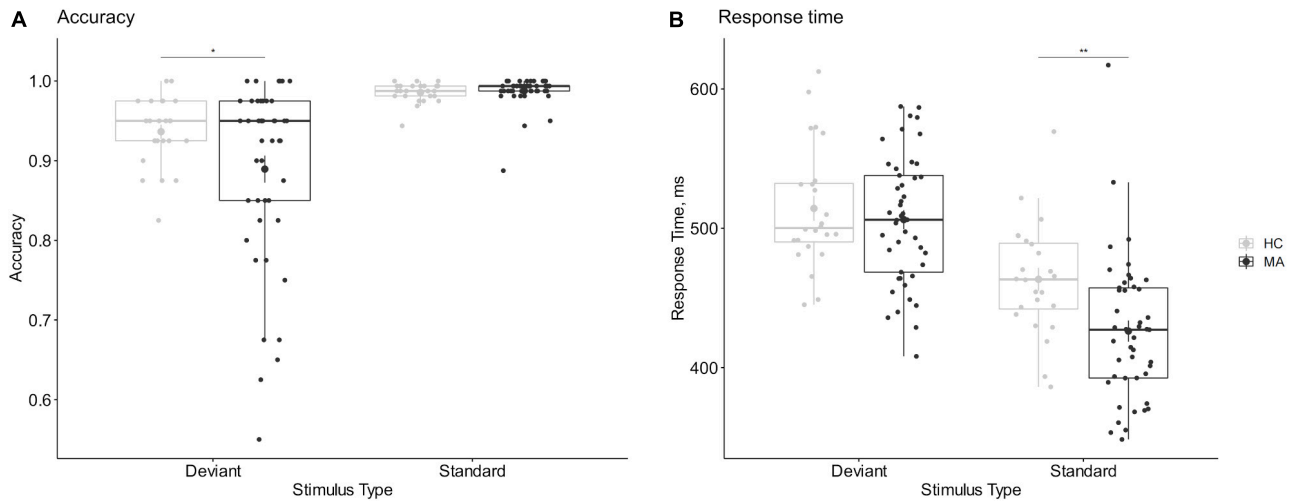

FIGURE 2 | Comparison of behavioral impulsivity between methamphetamine addicts and healthy controls. **(A)** The accuracy of 2-choice oddball task. **(B)** The response time of 2-choice oddball task. **(A)** The accuracy of 2-hoice oddball. **(B)** The response time of 2-choice oddball. MA refers to methamphetamine addicts, HC refers to healthy controls. *Refers to 2-sided $p < 0.05$. **Refers to 2-sided $p < 0.01$. Error bars show the standard error of the mean. Enlarged dots refer to means.

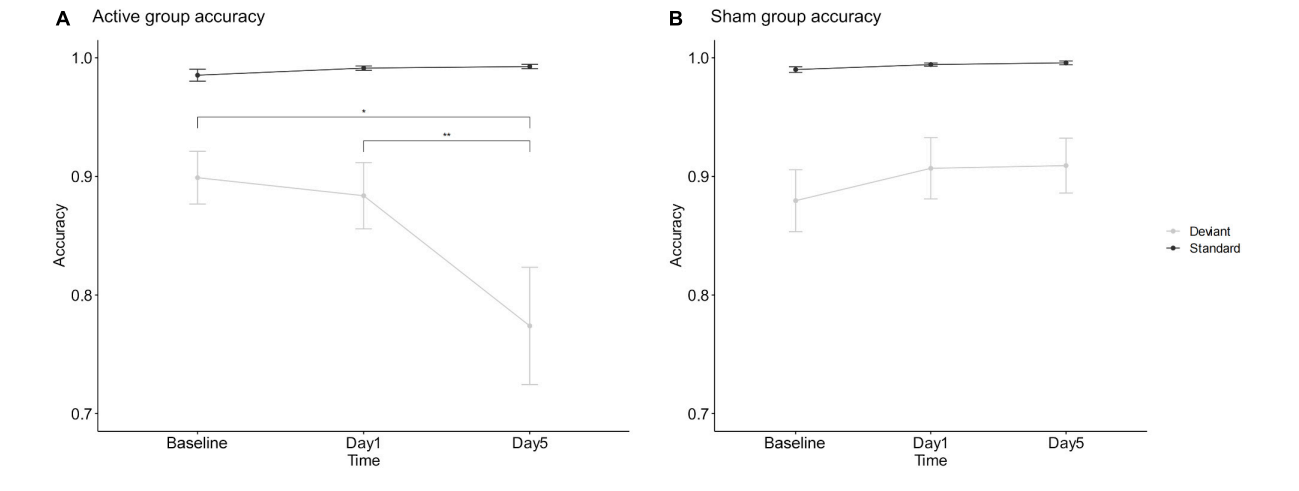

FIGURE 3 | Mean accuracy of active tDCS group **(A)** and sham group **(B)**. *Refers to 2-sided $p < 0.05$. **Refers to 2-sided $p < 0.01$. Error bars show the standard error of the mean.

(19), ADHD individuals (35), and gambling addicts (18), and suggested that using an appropriate tDCS protocol to stimulate DLPFC may effectively improve individuals' impulse control or behavioral inhibition ability. Based on these findings, the current study selected the DLPFC as a tDCS target and expected this protocol to significantly decrease behavioral impulsivity in methamphetamine addicts. However, counterproductive results were observed, with a significant increase in behavioral impulsivity of methamphetamine addicts. These results indicated that using tDCS to stimulate the DLPFC does an effective method to modulate behavioral impulsivity, but the protocol that used bilateral tDCS (right anodal/left cathodal) over DLPFC may lead to up-modulation.

Methamphetamine addicts have severely impaired DLPFC relative to healthy individuals (36). Specifically, methamphetamine addicts had significantly lower gray matter thickness in the DLPFC region (12, 37, 38) and lower activation during behavioral inhibition tasks (39). One recent study observed that bilateral tDCS (right anodal/left cathodal) over DLPFC increased the activation of executive control networks in the resting state of methamphetamine addicts and decrease the craving of methamphetamine addicts (25). However, given the extent of damage to the DLPFC in methamphetamine addicts, it is possible that activating this region may overdraw their DLPFC activity and subsequently decrease their impulse control. For example, a warm-up usually improves performance in healthy people, but the same warm-up may deplete sick person and his/her subsequent performance. This may be one potential reason why a similar protocol decreased impulsivity in healthy individuals (40) and individuals with other

psychological disorders (18) but led to counterproductive results in methamphetamine addicts.

Several limitations should be addressed in future work. First, although the current study used a 2-choice oddball task to assess impulsivity, no functional neuroimaging with tDCS intervention was collected, which led us unable to examine possible functional changes in the DLPFC. Therefore, future research can examine the current findings using neuroimaging techniques. Second, the current study measured baseline behavioral impulsivity in the HC group but they did not undergo tDCS intervention, leaving it not possible to examine how tDCS affects behavioral impulsivity in healthy people. In addition, the current study employed simple letters as stimuli (i.e., M and W) to ensure experimental control. However, previous studies have found that methamphetamine addicts have higher impulsivity to meth-related information (41, 42), so future work should consider selecting drug-related images as stimuli to improve the ecological validity of the study. Furthermore, the current study used only one active tDCS protocol (right anodal/left cathodal), which prevented us from exploring the effects of unilateral stimulation of the DLPFC on impulsivity in methamphetamine addicts. However, because the anodes and cathodes of tDCS may be associated with opposing neural effects (20) and the anodal tDCS may have different effects on the left DLPFC and the right DLPFC in methamphetamine addicts (22), additional tDCS protocols are needed in future studies to further investigate the lateralizing effects of tDCS on DLPFC function.

CONCLUSION

The current study evaluated the effect of bilateral tDCS (right anodal/left cathodal) over the DLPFC on behavioral impulsivity in methamphetamine addicts and found a counterproductively increased impulsivity after the 5-day intervention in methamphetamine addicts. The results suggested that using tDCS to stimulate the DLPFC is an effective method to modulate behavioral impulsivity, but as it is counterproductive, the current protocol may not be optimal and other protocols should be considered for the intervention of methamphetamine addicts in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in this 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 the Ethical Committee of the Institute of Brain and Psychology Science, Sichuan Normal University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XJ and JY conceived and designed the current study. XJ and CZ collected the data and statistical analysis. XJ, YT, and JY interpreted the data. XJ, YT, ZZ, and JY wrote the final manuscript. All authors contributed to reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.915440/full#supplementary-material

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SYSTEMATIC REVIEW
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Cannabinoids in the Treatment of Cannabis Use Disorder: Systematic Review of Randomized Controlled Trials

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Background: The prevalence of cannabis use and cannabis use disorders (CUD) has significantly increased over time. However, there are no approved pharmacological treatments for CUD. The aim of this study was to determine the efficacy and safety of various medical cannabinoids in the treatment of CUD.

Methods: We conducted a systematic review of randomized controlled trials which evaluated the therapeutic potential of medical cannabinoids in individuals with CUD and summarized the main study outcomes in terms of cannabis use, abstinence, withdrawal symptoms, craving, retention in treatment and adverse events.

Results: We identified eight trials with a total of 667 study participants. Dronabinol reduced cannabis withdrawal symptoms whereas nabiximols, cannabidiol and PF-04457845, a fatty acid amide inhibitor, also reduced cannabis use and improved abstinence, compared to placebo. Nabilone failed to demonstrate efficacy in the treatment of CUD. All medications were well-tolerated.

Conclusions: Cannabinoid receptor agonists, i.e., dronabinol and nabilone, showed only limited or no therapeutic potential in the treatment of CUD. In contrast, modulators of endocannabinoid activity, i.e., nabiximols, cannabidiol and PF-04457845, demonstrated broader efficacy which covered almost all aspects of CUD. Endocannabinoid modulation appears to be a promising treatment approach in CUD, but the evidence to support this strategy is still small and future research in this direction is needed.

Keywords: cannabis use disorder (CUD), cannabinoids, treatment, randomized controlled trial, endocannabinoid system (ECS), efficacy and safety

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INTRODUCTION

To date, cannabis is still the most widely used illicit drug worldwide, although meanwhile legalized for recreational purposes in several countries, with, in 2019, almost 4% of the global population (aged 15 to 64 years) having used cannabis at least once, the equivalent of about 200 million people (1). In Central and Western Europe as well as North America, the risk perception associated with

cannabis use is on the decrease, while regular cannabis use increased in the long-term, with a prevalence of 7.8 and 14.5%, respectively, in the adult population (1).

This development poses a notable public health issue as recreational cannabis use is associated with considerable adverse health effects, including cognitive deficits, motor impairment and psychosis (2). In addition, about 20–30% of the regular cannabis users have been found to develop a cannabis use disorder (CUD) over time (3). The risk of CUD increases with daily cannabis use, earlier age at first use and higher potency of cannabis (4). According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), CUD is defined by impaired control, social impairment, risky use, tolerance, and withdrawal (5). A recent meta-analysis reported that almost half of the regular or dependent cannabis users is affected by a cannabis withdrawal syndrome (6) which typically begins soon after cessation of use, peaks within a couple of days and lasts for up to 3 weeks (7). The cannabis withdrawal syndrome is characterized by craving, irritability, nervousness, sleep disorders, depressed mood and decreased appetite (8).

Although the number of people with CUD seeking treatment is increasing in Europe and North America, the overall utilization of CUD-specific treatments is relatively low and the majority of the affected individuals is untreated (9, 10). In the United States, CUD treatment seeking behavior and CUD treatment admissions among young adults (aged 18 to 24 years) have even declined (11). On the other hand, effective treatment options for CUD are limited and focus primarily on psychosocial interventions, including motivational enhancement therapy, cognitive behavioral therapy and contingency management (12). However, access to psychosocial interventions as well as coverage from insurance companies are often limited. Moreover, clinical trials showed that these treatments are cost-intensive and their abstinence rates are only modest and decline after treatment, raising the need for further therapeutic options, especially pharmacological treatments (13–16).

In the last two decades, numerous studies explored the potential of different medications with various pharmacological targets for the treatment of CUD. Human laboratory and clinical studies particularly aimed to identify pharmaceutical agents which are effective in the treatment of cannabis withdrawal syndromes, the maintenance of abstinence, the retention in treatment and the reduction of cannabis use. The most promising candidates included several antidepressants (e.g., bupropion, escitalopram, mirtazapine, nefazodone and venlafaxine), antipsychotics (e.g., quetiapine), anticonvulsants (e.g., valproic acid, gabapentin and topiramate) as well as lithium, buspirone and N-acetylcysteine (17, 18). Although some of these agents produced some benefits for distinct individual aspects in patients with CUD, none of these treatments has demonstrated sufficient empirical evidence to provide clear therapeutic recommendations and to achieve the approval for the treatment of CUD by the authorities, mainly due to insufficient study designs, sample sizes and outcome measures (19).

More recently, the endocannabinoid system and its components have been proposed to provide novel and unique systemic targets for the treatment of CUD. The primary constituent of cannabis, Δ^9-tetrahydrocannabinol (THC), produces its acute psychoactive effects via partial agonism at the cannabinoid type 1 receptor (CB1) in the central nervous system (20). Regular cannabis use is associated with the development of craving, tolerance and withdrawal symptoms which was related to a dysregulation of the endocannabinoid system, particularly to CB1 receptor downregulation and desensitization and reduced levels of the endocannabinoids N-arachidonoylethanolamide (AEA) and 2-arachidonoylglycerol (2-AG) (21). It was therefore suggested that the potentiation of endocannabinoid function by medical cannabinoids might serve as a promising treatment strategy for CUD (22). In this context, the following cannabinoids and cannabinoid preparations are of particular interest: dronabinol (THC), nabilone, a synthetic derivative of THC, cannabidiol (CBD), a natural inhibitor of the hydrolysis and reuptake of endocannabinoids as well as a negative allosteric modulator of the CB1 receptor, nabiximols, which contains a combination of THC and CBD at a ratio of ∼1:1, and PF-04457845, a synthetic inhibitor of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH).

This systematic review aims to summarize and discuss the main findings of randomized controlled trials (RCTs) evaluating the efficacy, safety and tolerability of different medical cannabinoids in the treatment of CUD.

METHODS

Information Sources and Search

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23), we systematically searched the PubMed/Medline database on November 6th, 2021, to identify all relevant studies. We also checked the reference lists of included studies and previous reviews. We used the following search terms: (cannabis OR marijuana OR marihuana OR THC OR tetrahydrocannabinol) AND (dependence OR withdrawal OR craving OR relapse) AND (treatment OR therapy OR medication OR replacement) AND (dronabinol OR nabilone OR nabiximols OR sativex OR cesamet OR FAAH OR fatty acid amide hydrolase OR CBD OR cannabidiol).

Eligibility Criteria

We defined the eligibility criteria following the Population-Intervention-Comparison-Outcomes-Study Design (PICOS) model (24):

- Population: adults (aged 18 years or older) with a diagnosis of cannabis use disorder (CUD) according to a valid diagnostic classification system, e.g., ICD-10 or DSM-V.
- Intervention: any pharmacotherapy with medical cannabinoids, i.e., dronabinol, nabilone, nabiximols, cannabidiol or endocannabinoid modulators, as monotherapy or in combination with another medication, with or without concomitant psychotherapy.
- Comparison: placebo.

TABLE 1 | Risk of bias assessment.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias
Levin et al. (26)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Levin et al. (27)	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Hill et al. (28)	Low risk	High risk	High risk	High risk	High risk	Low risk	High risk
Allsop et al. (29)	Low risk	High risk	Low risk	Low risk	Low risk	High risk	High risk
Trigo et al. (30)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lintzeris et al. (31, 32)	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Freeman et al. (33)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
D'Souza et al. (34)	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk

- Outcomes: reduction of cannabis use, maintenance of abstinence, reduction of withdrawal symptoms, reduction of craving, retention in treatment, safety, and tolerability.
- Study Design: randomized controlled studies.

Review articles, guidelines, expert opinions, study protocols, commentaries as well as human experimental and animal studies were excluded from this review.

Study Selection

At first, the titles and, if necessary, abstracts of all records were independently screened by two authors (CV, PR) and those articles which did not meet the eligibility criteria were excluded. Afterwards, the same two authors independently read the remaining articles in full-text which again were checked for the above-mentioned eligibility criteria. Only those articles which met the final eligibility criteria were included to the systematic review. All discrepancies were resolved through discussion and consensus.

Data Collection and Data Items

The same two authors extracted all relevant data from the included studies and abstracted the following items according to the PICOS model:

- Population: sample size, mean age, sex, cannabis use characteristics.
- Intervention: medical cannabinoid, dosage regimen, additional medication (if applicable), concomitant psychotherapy.
- Comparison: placebo regimen.
- Outcomes: measures of cannabis use (in grams or joints per day or week), duration of abstinence, measures of withdrawal symptoms, measures of craving, duration of retention in treatment, adverse events.
- Study Design: first author, year of publication, trial location, study characteristics (setting, duration, follow-up).

Risk of Bias Assessment

We assessed the risk of bias in every individual trial by using the Cochrane Collaboration's Risk of Bias Tool in randomized controlled trials (25) and assigned a rating of "low," "high" or "unclear" risk to each of the seven bias domains (randomization, allocation concealment, participant blinding, researcher blinding, selective reporting, attrition and other risks of bias). Based on the number of domains classified as "low risk," we also created an "overall" risk of bias. The risk of bias assessment is given in **Table 1**.

RESULTS

Study Selection

The systematic literature search revealed a total of 1,239 articles. After applying the above-mentioned eligibility criteria, 1,216 articles were excluded. In a second step, the two authors independently read the remaining 23 articles in full-text. Another 14 of the 23 articles were excluded because their study designs did not fulfill the criteria of a randomized controlled trial. The remaining nine articles met the final eligibility criteria (26–34). As two of the nine articles refer to one study (29/30), a total of eight studies was included to the systematic review. The corresponding PRISMA flow diagram is given in **Figure 1**.

Study Characteristics

Eight studies with a total of 667 participants were included to this review. Four hundred and thirty five participants (65.2%) completed the studies according to the protocol. Although all studies met the final eligibility criteria, they varied widely in terms of population characteristics, study design, interventions and outcomes. The mean age of the participants ranged from 26.4 to 37.1 years with a male predominance of 73% across all studies. One study categorically included only male participants (34).

All studies were randomized, double-blind and placebo-controlled clinical trials with a parallel design. Seven of the eight studies were outpatient-only trials with a study duration ranging from 4 to 12 weeks. One of them had a 4-weekly assessment interval (29/30) and five of them had an assessment frequency of one to two times per week (26–28, 30, 33). The other two studies included an inpatient treatment phase of up to 9 days (29, 34). An adjunctive psychosocial therapy was applied to all participants in all trials during the active treatment period except for one (34). Two studies had a follow-up assessment after 4 weeks (28, 29) and one study after 12 weeks (29/30). One of the trials included multiple follow-up assessments up to week 24 (33). The remaining four studies had no follow-up assessments (26, 27, 30, 34).

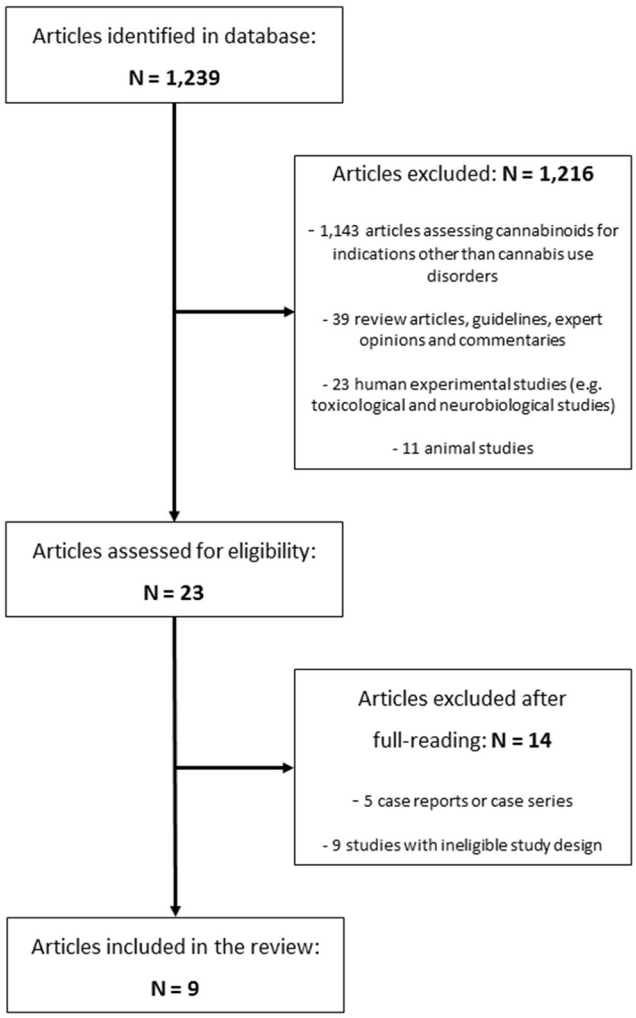

FIGURE 1 | PRISMA flow diagram of study selection.

All studies included participants with a CUD, as defined by the diagnostic criteria of the DSM-IV (27, 28, 30, 34), DSM-IV-TR (26, 29), DSM-V (33) and the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) (29/30). Four of the eight studies included participants with a previous quit attempt, two of which needed to have presented withdrawal symptoms (29, 34) and the other two studies did not state the need for having experienced withdrawal symptoms (29/30, 34). The remaining four trials did not consider previous attempts to quit cannabis use (26–28, 30). Dependence of other substances (except for nicotine and caffeine) was excluded in all studies. Unstable or severe axis I mental disorders were excluded from seven trials (26–32, 34) and one study only excluded patients with psychotic disorders (33).

Cannabis use at baseline and, if allowed by the study protocol, during the study was reported in different ways. Four studies rated cannabis use according to the number of days of use ranging from 25.7 to 28 days within the 28 days prior to baseline (26–28, 31, 32). Two studies used the cannabis weight, ranging from 6.0 to 22.98 g per week at baseline (29, 30), and one study registered the number of joints, i.e., 3.7 joints per day at baseline (34). Only one trial did not provide any information on the frequency or amount of cannabis use at baseline (33).

With regard to the study interventions, the eight studies applied five different cannabinoid preparations: dronabinol ($n = 2$) (26, 27), nabilone ($n = 1$) (28), nabiximols ($n = 3$) (29/30, 31, 32), CBD ($n = 1$) (33), and PF-04457845, a novel FAAH inhibitor ($n = 1$) (34). One of the two dronabinol studies (27) included it's combination with lofexidine, an alpha-2 noradrenergic agonist used in the treatment of opioid withdrawal (35).

All trials were carried out in developed countries: four single-center studies in the United States (26–28, 34), two multi-center studies in Australia (29/30, 32), one single-center study in Canada (30) and one single-center study in the United Kingdom (33).

Study Outcomes

The study characteristics and study outcomes are summarized in **Tables 2**, **3**.

Cannabis Use

Dronabinol: Dronabinol reduced self-reported cannabis use during an overall 12-week treatment phase compared to baseline. However, there were no differences in this aspect between the dronabinol and placebo group (26).

Nabilone: Nabilone had no effect on the magnitude of cannabis use compared to placebo (28).

Nabiximols: Nabiximols significantly reduced self-reported cannabis use during a 12-week treatment period compared to placebo (31). This finding remained significant at the week-24 follow-up after ceasing the treatment (32). However, another study did not find any between-group difference during a 12-week treatment phase (30) and a fourth study did not assess the use of cannabis as an outcome variable (29).

Cannabidiol: CBD 400 mg and 800 mg per day were more efficacious than placebo at reducing cannabis use during a 4-week treatment phase compared to placebo, as confirmed by decreased urinary THC-COOH:creatinine ratios (33). The reductions in cannabis use were maintained up to the final follow-up (week 16) in the CBD 400 mg group, but not in the 800 mg group.

FAAH inhibitor: PF-04457845 significantly reduced self-reported cannabis use during a 4-week treatment phase compared to placebo, as confirmed by reduced urinary THC-COOH concentrations (34).

Abstinence

Dronabinol: Dronabinol did not differ from placebo in the proportion of study participants who achieved two consecutive weeks of abstinence at the end of an 8-week maintenance phase (26). Dronabinol in combination with lofexidine also failed to demonstrate any difference in the proportion of participants with 3 weeks of abstinence during a 6-week maintenance phase compared to placebo (27).

Nabilone: not evaluated.

Nabiximols: One study reported no significant difference in the number of participants who have achieved a period of

TABLE 2 | Study characteristics.

Reference	Country	N	N*	Males (%)	Age (y)	Intervention	Maximum dose	Study design
Levin et al. (26)	USA	156	99	82.1	37.6	Dronabinol	40 mg/day	1-week outpatient placebo lead-in phase, followed by a 9-week treatment phase with a fixed dose schedule and a 2-week lead-out phase; no follow-up.
Levin et al. (27)	USA	122	67	68.8	35.1	Dronabinol + Lofexidine	Dronabinol 60 mg/day Lofexidin 1.8 mg/day	1-week outpatient placebo lead-in phase, followed by a 10-week treatment phase with a fixed-flexible dose schedule and a 1-week lead-out phase; no follow-up.
Hill et al. (28)	USA	18	12	66.7	26.4	Nabilone	2 mg/day	10-week outpatient treatment phase with a fixed dose schedule; follow-up after 4 weeks.
Allsop et al. (29)	Australia	51	35	76.5	35.4	Nabiximols	THC 86.4 mg/day CBD 80 mg/day	6-day inpatient treatment phase with a fixed dose schedule, followed by a 3-day washout phase; outpatient follow-up after 4 weeks.
Trigo et al. (30)	Canada	40	27	72.5	33.0	Nabiximols	THC 113.4 mg/day CBD 105 mg/day	12-week outpatient treatment phase with self-titrated study medication; target quit date for cannabis on day 21; no follow-up.
Lintzeris et al. (31, 32)	Australia	128	60	76.6	35.0	Nabiximols	THC 86.4 mg/day CBD 80 mg/day	12-week outpatient treatment phase with a 3-day dose induction period and weekly titrated doses; 12-week outpatient follow-up ($N = 55$).
Freeman et al. (33)	UK	82	77	72.0	26.4	Cannabidiol	A: 200 mg/day B: 400 mg/day C: 800 mg/day	4-week outpatient treatment phase with fixed doses; CBD 200 mg was stopped at interim analysis due to lack of efficacy; follow-up at weeks 6, 8, 12, 16, 20 and 24.
D'Souza et al. (34)	USA	70	58	100	28.2	PF-04457845	4 mg/day	5-(to 8)-day inpatient withdrawal phase, followed by a 3-week outpatient treatment phase with a fixed dose; no follow-up.

N, number of participants who were enrolled in the study. N, number of participants who completed the study. THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol.*

TABLE 3 | Main study outcomes.

Reference	Intervention	Cannabis use	Abstinence	Withdrawal symptoms	Craving	Treatment retention	Adverse events
Levin et al. (26)	Dronabinol	→	→	↓	N/A	↑	AEs: → SAEs: $N = 4$ (3 of them in the dronabinol group), not study-related
Levin et al. (27)	Dronabinol + Lofexidine	N/A	→	→	N/A	→	AEs: → SAEs: $N = 2$ (1 of them in the dronabinol + lofexidine group), not study-related
Hill et al. (28)	Nabilone	→	N/A	→	→	N/A	AEs: → SAEs: none
Allsop et al. (29)	Nabiximols	N/A	N/A	↓	↓	↑	AEs: → SAEs: $N = 1$ (in the placebo group)
Trigo et al. (36)	Nabiximols	→	→	→	→	N/A	AEs: → SAEs: none
Lintzeris et al. (31)	Nabiximols	↓	→	→	→	→	AEs: → SAEs: $N = 1$ (in the placebo group)
Lintzeris et al. (32)	Nabiximols	↓	↑	N/A	N/A	N/A	N/A
Freeman et al. (33)	CBD 200 mg CBD 400 mg CBD 800 mg	→ ↓↓	→ ↑↑	N/A→ ↓	N/A N/A N/A	N/AN/AN/A	All doses: AEs: → SAEs: none
D'Souza et al., 2018	PF-04457845	↓	N/A	↓	N/A	N/A	AEs: → SAEs: none

↑, significant increase compared to placebo; → , non-significant effect compared to placebo; ↓, significant reduction compared to placebo; N/A, not evaluated; AEs, adverse events; SAEs, serious adverse events; CBD, cannabidiol.

abstinence from cannabis of at least 4 weeks during a 12-week treatment phase with nabiximols compared to placebo (31). However, there was a significantly higher proportion of participants of the nabiximols group than the placebo group of the same study sample who reported abstinence in the previous 4 weeks at the week-24 follow-up (32). In another study, nabiximols did not differ from placebo regarding abstinence rates at the end of a 12-week treatment phase (30). A fourth study did not evaluate abstinence rates (29).

Cannabidiol: CBD 400 mg and 800 mg increased the number of days per week with abstinence from cannabis during a 4-week treatment phase compared to placebo, as assessed by self-reports (33).

FAAH inhibitor: not evaluated.

Withdrawal

Dronabinol: Dronabinol showed a greater reduction of cannabis withdrawal symptoms during an overall study period of 12 weeks, compared to placebo (26). On the other hand, dronabinol combined with lofexidine showed no significant effect on weekly cannabis withdrawal scores during a 10-week study period (27).

Nabilone: Nabilone did not differ from placebo in the reduction of cannabis withdrawal symptoms during a 10-week treatment period (28).

Nabiximols: One study found a significant decrease in withdrawal symptoms by nabiximols during a 6-day treatment phase compared to baseline, while the withdrawal scores in the placebo group increased (29). Moreover, the duration of the withdrawal syndrome was shorter and the peak of symptoms occurred earlier. Two studies reported a reduction of withdrawal symptoms during the treatment with nabiximols (up to 12 weeks), but without any significant differences between nabiximols and placebo (30, 31).

Cannabidiol: CBD 800 mg, but not 400 mg, was more efficient in reducing cannabis withdrawal symptoms during a 4-week treatment phase and follow-up, compared to placebo (33).

FAAH inhibitor: PF-04457845 significantly reduced symptoms of cannabis withdrawal during about a week of forced abstinence, compared to baseline and placebo (34). Consistently, the PF-04457845 group also reported less depression, irritability, anxiety and sleep disturbances which are symptoms likely related to cannabis withdrawal.

Craving

Dronabinol: not evaluated.

Nabilone: Nabilone and placebo reduced cannabis craving during a 10-week treatment phase. However, there were no significant treatment group differences at either the end of treatment or the end of a 4-week follow-up period (28).

Nabiximols: One study reported a significantly greater reduction of cannabis craving during a 6-day treatment episode in the nabiximols group compared to the placebo group (29). Two studies reported a reduction of cannabis craving during the treatment with nabiximols and placebo (up to 12 weeks), but with no significant between-group differences (30, 31).

Cannabidiol: not evaluated.

FAAH inhibitor: not evaluated.

Retention in Treatment

Dronabinol: The retention in treatment at the end of an 8-week maintenance phase was significantly higher in the dronabinol group compared to the placebo group (26). However, the combination of dronabinol and lofexidine showed no difference from placebo in the retention rate at the end of a 6-week maintenance phase (27).

Nabilone: not evaluated.

Nabiximols: Nabiximols was associated with a higher rate of treatment retention at the end of a 6-day medication phase compared to placebo (29). Another study could not confirm a difference between the nabiximols and the placebo group regarding the retention in treatment (31), and one study did not report on this outcome variable (30).

Cannabidiol: not evaluated.

FAAH inhibitor: not evaluated.

Adverse Events

Dronabinol: The maximum dose of 40 mg per day was well tolerated with no differences between dronabinol and placebo regarding the number of adverse events (26). Four serious adverse events were reported (hospitalization because of worsening of diabetes, worsening of chronic asthma, stomach virus and altercation with the police), three in the dronabinol and one in the placebo arm, which were not deemed to be study-related. Similarly, there were no significant differences between dronabinol in combination with lofexidine and placebo regarding the overall number of adverse events (27). There were two serious adverse events (hospitalization because of abdominal pain, admission to a detoxification program), one in each study arm, which were not considered to be related to the study procedure.

Nabilone: Doses of 2 mg were well-tolerated. All reported adverse events were mild to moderate and no serious adverse event was recorded (28).

Nabiximols: No between group differences in adverse events were reported (29–31). In the three studies, two serious adverse events occurred, each in the placebo group [hospitalization for suicidal ideation (31) and threat of suicide (29)].

Cannabidiol: CBD at 400 mg and 800 mg per day was well tolerated. There was no difference in the number of mild or moderate adverse events between both dosage groups and the placebo group. No serious adverse events were recorded (33).

FAAH inhibitor: PF-04457845 was well tolerated. The recorded adverse events were mild and the number of adverse events did not differ from the placebo group. There were no serious adverse events and the FAAH inhibitor did not influence the dropout rate (34).

DISCUSSION

This study aimed to systematically review the current literature on the use of cannabinoids in the treatment of CUD and to summarize the main findings in terms of efficacy, safety and tolerability provided by randomized controlled trials. We identified eight studies which examined the effects of five cannabinoid preparations on specific clinical outcome variables,

i.e., cannabis use, abstinence, withdrawal, craving, retention in treatment and adverse events. Regarding their, at least in part, different mechanisms of action, we could classify the cannabinoids to two therapeutic strategies: (A) agonist substitution and (B) endocannabinoid modulation.

The agonist substitution therapy, also known as replacement therapy, has been proven to be effective in various substance use disorders, particularly in nicotine and opioid dependence. It therefore appeared obvious to test cannabinoid receptor agonists in the treatment of CUD. In this respect, three cannabinoid preparations were of particular interest, dronabinol, nabilone, and nabiximols. Dronabinol and nabilone are currently used as a second line treatment for patients with AIDS/cancer cachexia and for chemotherapy patients experiencing nausea or vomiting (37, 38). Nabiximols is used in the treatment of central neuropathic pain in multiple sclerosis and as an adjuvant analgetic in adults with advanced malignancy (36). In several human laboratory studies, CB1 receptor agonists have been shown to alleviate symptoms of cannabis withdrawal and to reduce relapse in patients with CUD (39, 40).

As expected, dronabinol attenuated cannabis withdrawal symptoms and improved retention in treatment but failed to reduce cannabis use and to improve abstinence, which was the primary outcome of the two studies (26, 27). It was suggested that the CB1 receptor-agonistic properties of dronabinol successfully counteracted the development of withdrawal symptoms, but the low motivation to quit among the participants might have been responsible for the lack of an effect on cannabis use and abstinence. The authors therefore concluded that the participants would have benefited from a longer maintenance period in order to better promote a motivation for sustainable change. Similarly, nabiximols improved withdrawal symptoms, craving and treatment retention, but, in contrast to dronabinol, also reduced cannabis use and improved abstinence (29, 31, 32). This significant difference from dronabinol in the therapeutic profile might be explained by the additional presence of CBD for which "anti-addictive" action has been described recently, see further below (41). On the other hand, nabilone failed to demonstrate any beneficial effects on cannabis use, withdrawal or craving. In this context, the authors speculated whether the dose of nabilone might have been too low in order to display therapeutic efficacy in CUD (28). Moreover, the sample size of 18 participants of whom only 12 completed the overall treatment phase seems too small to draw any robust conclusion on nabilone's efficacy.

The modulation of the endocannabinoid system is a relatively novel approach in the treatment of CUD (22). The endocannabinoid system consists of specific cannabinoid receptors, i.e., the CB1 and CB2 receptor, their primary endogenous ligands AEA and 2-AG, and the AEA- and 2-AG-degrading enzymes FAAH and monoacylglycerol lipase (MAGL) (20, 42). At the molecular level, endocannabinoids play a crucial role in the regulation of various neurotransmitter systems, including the dopaminergic mesolimbic reward pathways (43). It is therefore suggested that the modulation of the endocannabinoid system might have the potential to normalize the dopamine signaling which is typically disrupted by heavy cannabis use, and, thus, appear to be a promising target in the treatment of CUD.

In this context, CBD, the second most abundant constituent of cannabis, is a cannabinoid of substantial interest with regard to the treatment of CUD (41). CBD has only minimal direct action at cannabinoid receptors but primarily acts as an inhibitor of the hydrolysis and reuptake of endocannabinoids (44) as well as a negative allosteric modulator of the CB1 receptor (45), thereby counteracting the acute psychoactive effects of THC (46). As a modulator of the endocannabinoid system, CBD reduced cannabis use, improved abstinence and attenuated withdrawal symptoms (33). The reductions in cannabis use at week-16 follow-up was only evident in the 400 mg-group and the reductions in cannabis withdrawal was only evident in the 800 mg-group. In this case, it can be assumed that the enhancement of the endocannabinergic activity might have contributed to the beneficial effects of CBD.

Another approach for the treatment of CUD also referred to the modulation of the endocannabinoid system by the inhibition of FAAH. In this context, the selective FAAH inhibitor URB597 has been reported to attenuate withdrawal symptoms in an animal model of CUD by increasing AEA concentrations (47). Moreover, mice with reduced FAAH expression due to a genetic variation have been shown to be less likely to develop CUD than the wild-type carriers (48). PF-04457845 is a novel and highly selective and potent human FAAH inhibitor which, so far, was mainly tested in patients with diverse pain syndromes (49). The only study in the present review which evaluated the efficacy of PF-04457845 in CUD showed reduced cannabis use and cannabis withdrawal symptoms compared to placebo (34). The authors suggested that the increase of endocannabinoid concentrations by selective FAAH inhibition might have been the key mechanism contributing to this outcome.

LIMITATIONS

The results of the studies summarized in this review need to be interpreted with caution. First of all, the studies showed a large variety, particularly with regard to population characteristics (low motivation vs. high motivation to quit cannabis use), study setting (inpatient vs. outpatient), study design (forced abstinence vs. harm reduction), concomitant interventions (psychosocial therapy vs. no psychosocial therapy) and operationalization of outcome measures (e.g., cannabis use as assessed by the frequency or the amount of use). These differences impede a meaningful comparison of the efficacy of different cannabinoids. Second, the drop-out rate of about one third among all studies was relatively high which might have affected the significance of the respective study results. Third, specific populations were underrepresented, such as women, older people and individuals from different ethnicities or with comorbid mental disorders or other substance use disorders. In this respect, the study results are less generalizable to other populations and do not picture the real world. Finally, the effects of the different cannabinoids on the various outcome variables

were rather modest, most probably due to the relatively small sample sizes.

CONCLUSIONS

The agonist substitution (replacement) approach with the CB1 receptor agonist dronabinol showed efficacy in the reduction of cannabis withdrawal symptoms but it was not able to demonstrate an influence on cannabis use or abstinence. In contrast, the modulation of the endocannabinoid system by CBD or the selective FAAH inhibitor PF-04457845 seems to be efficacious for both reducing withdrawal symptoms and improving cannabis use and abstinence. As endocannabinoid modulators, compared to CB1 receptor agonists, also produce lower abuse liability and less intoxication, they appear to be a promising group of drugs for the treatment of CUD (22). However, the evidence is at this time too weak to support any specific medication. Future studies should include greater sample sizes, more diverse populations, longer treatment periods and head-to-head comparisons.

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

PR designed the study. CV and PR performed the literature searches, screened the studies, and wrote the first draft of the manuscript. CV, NS, UB, and PR critically contributed to the discussion and approved the final version of the article. All authors contributed to the article and approved the submitted version.

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Dysregulated Methylation Patterns in Exon IV of the Brain-Derived Neurotrophic Factor (BDNF) Gene in Nicotine Dependence and Changes in BDNF Plasma Levels During Smoking Cessation

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Introduction: Several studies reported dysregulated protein levels of brain-derived neurotrophic factor (BDNF) in smokers and during cessation. However, the epigenetic regulation of the BDNF gene has not yet been investigated. We measured the plasma levels of BDNF and the epigenetic regulation of exon IV of the BDNF gene in smokers compared to healthy controls over a cessation period of 14 days.

Method: We measured BDNF plasma levels and BDNF promoter methylation in 49 smokers and 51 non-smokers at baseline, day 7, and day 14 of smoking cessation. Mean methylation levels of 11 Cytosine Guanosine dinucleotides of exon IV of the BDNF gene were determined *via* bisulfite sequencing.

Results: BDNF plasma and methylation levels were significantly lower in healthy controls when compared with smokers across all time points. BDNF levels for smokers decreased significantly during the cessation period. Comparing the sexes, female smokers showed significantly lower plasma BDNF levels than healthy controls at baseline and over 14 days of cessation. Male and female smokers showed significantly higher mean methylation rates than non-smokers at baseline. In male smokers, mean methylation levels decreased significantly during the cessation period.

Conclusion: Our findings replicate the findings of previous studies that BDNF plasma levels are altered in smokers. Furthermore, BDNF expression and gene methylation are altered during the first 14 days of cessation. Our novel findings of dysregulated methylation patterns in exon IV of the BDNF gene further support the thesis that BDNF plays a role in nicotine dependence.

Keywords: tobacco dependence, addiction - smoking, addiction, epigenetic, addict behavior

INTRODUCTION

Cigarette smoking is one of the leading preventable causes of related chronic diseases and deaths worldwide (1). Nicotine is the main psychoactive component of tobacco that affects many neurotransmitter systems and other factors such as brain-derived neurotrophic factor (BDNF) (2). BDNF, a member of the neurotrophin family (3), is abundantly expressed in the central and peripheral nervous systems (4, 5) as well as peripheral tissue such as platelets (6). It is involved in many critical neuronal processes like developing and regulating neuro (7)-, glio (8)- and synaptogenesis (9). As a promoter of neurite growth, it fosters physiological neuronal system development (7).

Brain-derived neurotrophic factor also modulates diverse neurotransmitter systems like glutamatergic, dopaminergic, and serotonergic systems (10). Peripheral BDNF can be analyzed in plasma and serum and some studies reported a positive correlation with brain BDNF (11, 12). Thus, depending on the context, changes in peripheral BDNF can, to a limited extent, be used as surrogates of brain changes. Earlier studies supported evidence that BDNF plays a crucial role in several substance addictions, such as alcohol, cocaine, and methamphetamine addiction (13). In the context of nicotine dependence, several animal studies suggest that BDNF is functionally involved (2). Previous studies in humans showed that peripheral BDNF levels are altered in smokers compared to non-smokers. While the first two studies showed a decrease in BDNF in smokers (14, 15), all subsequent studies observed an increase in BDNF protein levels in smokers (16–18).

Furthermore, studies have also investigated methylation of BDNF promoter I in major depressive disorder, showing an association between neurocognitive performance and two BDNF SNPs, while methylation levels mediated this effect at specific sites of promoter I (19). In another study, higher BDNF methylation levels at exon I and exon IV were associated with major depression (20). According to Ikegame et al., patients suffering from mental disorders generally show decreased neural BDNF levels, which are often – but not always – associated with DNA methylation at specific BDNF promoter regions (21). Hence, we assumed that changes in plasma BDNF levels would be related to changes in the methylation status of the BDNF promoters. However, to the best of our knowledge, no studies have investigated the epigenetic regulation of the BDNF gene in the context of nicotine dependence and smoking cessation. We hypothesized that plasma BDNF levels would be associated with methylation levels at exon IV promoter of BDNF and that changes in protein levels would be associated with changes in methylation levels over the cessation period. This study investigates plasma BDNF levels and methylation rates of exon IV of the BDNF gene in smokers compared to healthy non-smokers at baseline and over a cessation period of 14 days.

MATERIALS AND METHODS

This study adhered to the Declaration of Helsinki and was approved by the local Ethics Committee of Hannover Medical School (approval number: 6695). We included 49 smokers with nicotine dependence as defined by the International Classification of Diseases and Diagnostics (ICD-10) and Statistical Manual of Mental Disorders (DSM IV) (**Table 1**). As controls, 51 healthy non-smokers were recruited. All participants in this study gave written informed consent. Exclusion criteria were concomitant psychiatric illness, other substance or alcohol abuse or dependence, cerebral ischemia, cerebral hemorrhage, epilepsy, cardiovascular and renal diseases, age under 18 years, pregnancy, and nicotine replacement therapy. Inclusion criteria were age 18–65 years and current smoker (minimum seven cigarettes per week or one cigarette a day). The severity of nicotine addiction was measured using the Fagerström-Test, while craving was assessed using the Questionnaire of Smoking Urges (QSU).

All smokers underwent a detailed physical examination, routine laboratory testing, and urine drug screening. Fasting blood samples and cotinine to check for relapse were drawn from nicotine-dependent smokers and the controls on days 1, 7, and 14 (t0, t7, t14) of abstinence between 8:00 and 10:00 a.m. We choose a period of 2 weeks since withdrawal symptoms tend to peak during the first week and can last up to four more weeks (22). In a different study, the authors

TABLE 1 | Demographics.

		Age			BMI			Cigarettes/Day			QSU score			Fagerström		
	Count (*N*)	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*
Controls																
Male	25	25.17	7.54	24	24.09	2.70	25									
Female	26	27.42	7.12	26	22.17	3.20	26									
Smokers																
Male	29	29.56	10.08	25	26.61	4.12	25	11.40	7.26	25	70	28	29	2	2	29
Female	20	33.44	9.56	18	23.53	3.69	20	12.72	7.89	18	64	17	20	3	2	20

Some smokers and controls did not report age and BMI. For our Analysis of promoter methylation and BDNF plasma levels we included all samples with valid values (49 smokers vs. 51 controls).

BMI, body mass index; N, number; QSU, questionnaire of smoking urges; SD, standard deviation.

have observed changes in mean methylation of the BDNF promoter over 14 days in smokers during alcohol withdrawal therapy (23). All blood samples were anti-coagulated with sodium EDTA. Plasma was separated in a centrifuge at 4,000 g, and the aliquots were stored at −80°C. BDNF plasma levels were measured using the Quantikine Total BDNF ELISA (Cat# DBNT00, R&D Systems, Minneapolis, USA). As the sample count exceeded assay size, we decided to measure samples from equal time points on one plate, applying the same standard to every measurement. DNA for methylation analysis was extracted from blood using the NucleoMag 200 kit (Macherey&Nagel, Düren, Germany). Bisulfite conversion and purification were performed using the EpiTect®96 Bisulfite Kit 142 (Qiagen, Hilden, Germany) following the manufacturer's recommendations. A detailed protocol of bisulfite sequencing and determination of methylation rates is provided in **Supplemental File 1**.

BDNF Exon IV

The BDNF gene has 11 exons and nine functional promoters (24). We investigated BDNF exon IV since it has been extensively studied in psychiatric research, mainly in the context of depression (25).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences 26 (SPSS, IBM, Armonk, NY, USA). GraphPad Prism 9 (San Diego, California, USA) was used for data illustration. As normality was not present in both methylation data and ELISA measurements, we used the Kruskal–Wallis Test to test for differences across controls and smokers. For pairwise comparisons, we performed Dunn's *post hoc* test with Bonferroni correction for multiple comparisons in independent samples to compare healthy controls with smokers. To measure changes across time points in the smokers' groups we used Friedman's Test for dependent samples, followed by Dunn's Test for pairwise comparison while controlling for multiple testing using Bonferroni correction. For bivariate correlations, we applied the Spearman method as a non-parametric option, accordingly.

RESULTS

BMI

BMI was significantly lower in controls compared with smokers across all time points (H (3) = 13.45, $P = 0.004$). Furthermore, BMI was significantly lower in controls when compared with t0, t7, t14 (H (1) = −29.76, $P = 0.04$; H (1) = −33.05, $P = 0.015$; H (1) = −32.24, $P = 0.014$). In males, BMI was significantly lower in controls when compared to smokers across time points (H (3) = 10.55, $P = 0.014$), while there was no difference for females. Furthermore, BMI was significantly lower in male controls when compared with t0, and t14 (H (1) = −21.87, $P = 0.046$; H (1) = −21.92, $P = 0.042$).

Peripheral BDNF Levels

BDNF plasma levels were significantly lower in controls when compared to smokers across timepoints (H (3) = 16.56, P = 0.001). Furthermore, BDNF levels were significantly lower in controls when compared with t0, t7, t14 ($z = -42.64$, $P = 0.001$; $z = -35.50$, $P = 0.011$; $z = -31.30$, $P = 0.035$). In smokers, no significant change was observed during withdrawal.

In females, BDNF plasma levels were significantly lower in controls when compared to smokers across timepoints (H (3) = 26.79, $P < 0.001$). While there was no difference for males, BDNF levels were significantly lower in female controls when compared with female smokers at t0, t7, t14 ($z = -33.09$, $P < 0.001$; $z = -29.17$, $P = 0.001$; $z = -26.82$, $P = 0.002$; see **Figure 1**).

BDNF levels decreased significantly during the cessation period (χ^2 (2) = 7.46, $P = 0.024$). Using pairwise comparison, BDNF levels were significantly lower at T14 compared with T0 ($P = 0.04$; see **Figure 1**).

In females, BDNF levels decreased significantly during the cessation period (χ^2 (2) = 6.10, $P = 0.047$). There was no significant difference when comparing different timepoints after the Bonferroni correction (see **Figure 1**).

Methylation Analysis

As a first step, we investigated differences in methylation levels at specific CpG islands of the promoter region of exon IV. Comparison of specific CpGs did reveal no significant differences between healthy controls and smokers (see **Supplementary Figure S1**). We further compared mean methylation of exon IV promoter for the two groups and genders. Mean methylation levels were significantly lower in controls when compared to smokers across time points (H (3) = 21.07, $P < 0.001$). Furthermore, mean methylation significantly lower in controls when compared with t0, t7, t14 ($z = -49.56$, $P < 0.0001$; $z = -30.55$, $P = 0.044$; $z = -38.59$, $P = 0.004$). In smokers, no significant change was observed during withdrawal.

In males and females, mean methylation levels were significantly lower in controls when compared to smokers across time points (H (3) = 9.65, $P = 0.022$; H (3) = 18.63, $P < 0.001$, respectively). Furthermore, mean methylation levels were significantly lower in female controls when compared with female smokers at t0, t7, t14 ($z = -24.09$, $P = 0.006$; $z = -27.69$, $P = 0.001$; $z = -22.76$, $P = 0.012$) and in male controls when compared with male smokers at t0 (H (1) = −23.690, $P < 0.05$; **Figure 2**).

Across smokers, there was no significant change in mean methylation levels during the cessation period. In male smokers, mean methylation levels decreased significantly during the cessation period (χ^2 (2) = 6.07, $P = 0.048$). Furthermore, using the non-parametric 'Dunn's test, mean methylation was significantly lower at T7 when compared with T0 ($P = 0.045$). Of note, there was no difference between T0 and T14 as well as between T7 and T14 (**Figure 2**).

Association Between Craving and Mean Methylation

We used Spearman's correlation analysis to analyze a relationship between mean methylation, BDNF plasma levels, and questionnaire of smoking urges (QSU) scores at all three time points. Here, we found a positive association between the

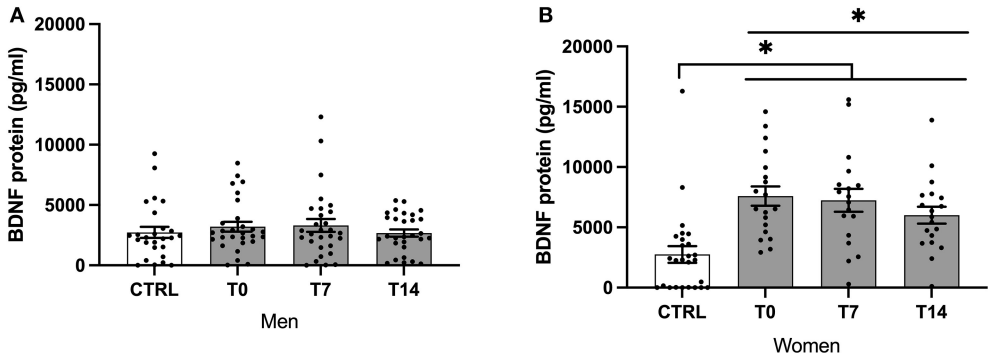

FIGURE 1 | BDNF protein levels of male **(A)** and female **(B)** smokers at baseline, day 7 and day 14 of cessation vs. healthy controls. BDNF, brain-derived neurotrophic factor; CTRL, healthy controls; T0, first day of cessation; T7, day 7 of cessation; T14, day 14 of cessation. Significant differences are indicated by asterisks ($P \leq 0.05$*).

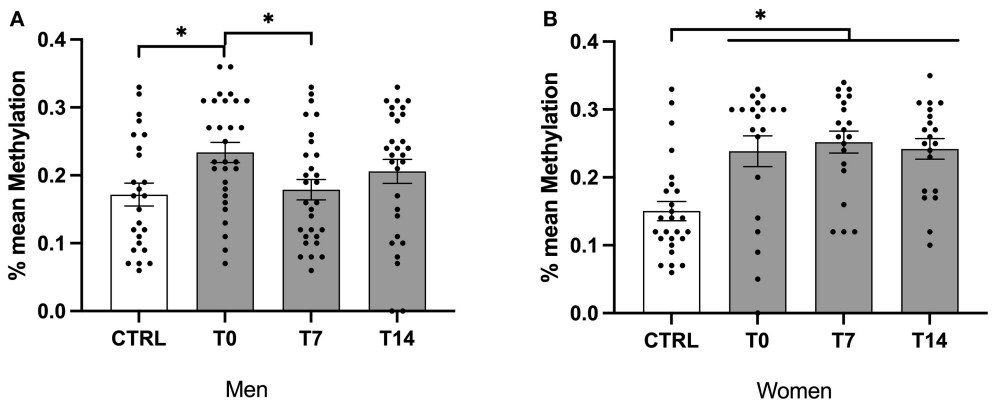

FIGURE 2 | Mean methylation levels of exon IV in BDNF gene of male and female smokers at baseline, day 7 and day 14 of cessation vs. healthy controls. BDNF, brain-derived neurotrophic factor; CTRL, healthy controls; T0, first day of cessation; T7, day 7 of cessation; T14, day 14 of cessation. Significant differences are indicated by asterisks ($P \leq 0.05$*). BDNF protein levels of male **(A)** and female **(B)** smokers at baseline.

QSU (subtest 2) and the total QSU score with mean methylation ($r(145) = 0.228$, $P = 0.06$; $r(145) = 0.191$, $P = 0.02$, respectively).

Association Between Addiction Severity and Methylation

We used the Fagerström test for nicotine dependence (FTND) to assess how BDNF promoter methylation and protein levels related to addiction severity (26). Nonparametric correlation analysis revealed a significant correlation of both methylation (r (47) = 0.322, $P = 0.024$) and protein levels (r (47) = 0.362, $P = 0.011$) at time point t14. Plotting these correlations, however, did not reveal a significant association between addiction severity and methylation ($r > 0.098$; **Supplementary Figure S2**). Also, using the classification from the previous study [1 (FTND < 3), 2 (FTND = 3–4), 3 (FTND > 4)], groups did not differ significantly when put in relation to either protein levels or mean promoter fragment methylation (data not shown).

Correlation Between BMI, Mean Methylation and BDNF Levels

Using Spearman's Correlation Coefficient, BMI showed no association with BDNF plasma levels and mean methylation across the whole sample (controls, smokers at t0, t7, and t14).

DISCUSSION

As we expected BDNF levels to be altered by addiction and within the cessation period of 14 days, we investigated the effect of smoking cessation on plasma BDNF levels and methylation of exon IV of the BDNF gene. BDNF plasma and methylation levels were significantly higher in smokers when compared with controls across all time points. Mean methylation was significantly higher in smokers when compared with healthy controls across all time points. Also, female smokers showed significantly lower plasma BDNF levels than healthy controls at baseline and over 14 days of cessation.

Dysregulation of BDNF in Nicotine Dependence

Our findings indicate that BDNF could be dysregulated in smokers, while there was no significant change in methylation rates during cessation in both sexes across all time points. We found significant differences in males when comparing day 1 and 7 methylation percentages. Meanwhile, we observed significantly decreasing BDNF protein levels, even though we found no corresponding change in methylation, indicating a complex regulation of which methylation is only one contributing

influence. In male smokers, mean methylation levels decreased significantly during the early cessation period (day 1 and 7) and then regressed to the first value. In female smokers, BDNF levels decreased significantly over the whole cessation period. Taken together, our results suggest that BDNF plasma expression and mean methylation are influenced by smoking as well as smoking cessation.

Interestingly, we found a positive association between mean methylation levels and craving across all time points. Even though this finding points to a possible influence of methylation levels on craving, the effect sizes are only small. We would therefore interpret this very interesting result as a trend that needs future investigations.

Furthermore, BDNF could be involved in the steps of a cascade of several dysregulated pathways involved in nicotine dependence. Several studies investigated the effect of smoking on peripheral BDNF levels (14–18), while most studies showed an increase of peripheral BDNF in smokers compared to non-smokers, which is in line with our findings of elevated BDNF levels in smokers. Further investigation is needed to validate methylation and plasma expression levels of BDNF over a longer period than 14 days, especially to investigate whether BDNF levels approach levels of non-smokers.

Influence of BMI on BDNF

There is evidence that plasma BDNF levels vary in relation to body weight in females (27). In the present study, BMI levels were not associated with plasma BDNF levels and significantly lower in controls compared with smokers. Since our assumptions for performing parametric tests were not met, we could not perform an analysis of covariance to identify a possible influence of BMI on BDNF levels. In line with previous findings, one possible explanation is that BMI differences could explain our varying results. However, since several factors influence BMI while BDNF seems to be associated with addictive behavior predominantly, it is possible that the changes could be due to cessation. This is also highlighted by the fact that BDNF levels decreased significantly during the observation period.

Factors Influencing BDNF Expression

Increasing evidence has shown that sociodemographic variables and lifestyle factors such as food and alcohol intake influence peripheral BDNF levels (28). In one study on BDNF, the authors concluded that future studies should consider correcting for the time of blood withdrawal, storage, urbanicity, age, sex, smoking status and food and alcohol intake (28). In the present study, we accounted for some of the mentioned variables by performing blood withdrawal and immediately (>2 h) storing all samples in a specific manner (s. methods). As we could not include the potential influence of age and sex in the main analysis, we validated the role of these variables for methylation by correlation analysis and could not see an influence (data not shown). Furthermore, we did not specifically assess urbanicity, food, or alcohol intake. Regarding sex, one study on the association between BDNF levels and major depressive disorder reported that, in females, BDNF levels decline with age while remaining stable in males. Furthermore, after controlling for gender and age, the assays showed lower serum BDNF levels being associated with higher depression scores. Interestingly, in this study the effects remained significant after correction for withdrawal time and smoking (29). Here we found peripheral BDNF levels to decrease during the cessation in females but not in males. In conjunction with the discussed evidence, our results suggest possible gender-specific differences. Due to the non-parametric nature of our data, we did not conduct further analysis to identify a possible influence of age and gender on protein or methylation levels. Respectively, one study has argued that BDNF levels are generally not normally distributed (30), and thus Gass and Hellweg (31) conclude that small studies using parametric tests could therefore be misleading.

BDNF Methylation or Expression and Addiction Severity

Both QSU and FTND show slight aspects of association upon initial correlation but fail to reveal substantial predictive value for both addiction severity and craving. This is in part due to the small cohort, where stratification is limited. With BDNF changes being at the periphery of the regulatory processes that are involved in reward circuitry regulation, variance is likely to be increased and therefore requiring bigger cohorts to justify reliable interpretation.

The Role of Peripheral BDNF Levels for Regulation in the Brain

From studies in rodents, peripheral and brain BDNF protein levels appear to correlate (11, 12). For the human brain, levels are different in distinct brain areas (32) and research has shown both evidence supporting and contradicting a correlation between central and peripheral BDNF-levels (33). We, therefore, do not associate methylation and peripheral expression levels with the situation in the addicted brain. Of note, circulating BDNF levels have been suggested to be associated with cognitive function, with lower levels being found in patients with amnestic mild cognitive impairment (34). Thus, differences in peripheral levels could be partly explained by molecular differences leading to cognitive function. This is important since a prospective study by Vermeulen et al. (35) on the association between smoking behavior and cognitive function in patients with psychosis, their siblings, and healthy controls has shown that smoking is associated with poorer cognitive function in each group compared with nonsmoking. The mean age in our study was similar to that in this study by Vermeulen et al. (35), highlighting this critical factor influencing BDNF levels. In contrast, a recent review concluded that BDNF is dysregulated in many pathological conditions and cannot be regarded as a valid biomarker but a marker related to mnemonic symptoms' occurrence or progression (32).

Concerning peripheral BDNF levels in major depression, one review has highlighted platelet function as a possible confounding factor influencing BDNF measurement, with platelets being the major source of peripheral BDNF (33). Since

cigarette smoke is well known to affect platelet function (36–38), a recent study has shown that platelet-derived BDNF regulates tissue factor expression and that cigarette smoke stimulates pro-atherothrombotic states (39). Also, human platelets treated with an aqueous extract of cigarette smoke released BDNF in a dose-dependent manner (39). Therefore, smoking cessation might influence platelet function and, in consequence, BDNF-level expression, while the kinetics of these effects remain unclear. The significantly higher BDNF levels we found in smokers could be caused by the effect of smoking on platelet function. Furthermore, it seems possible that the normalization of platelet function could partly explain the significant change in BDNF levels during cessation groups.

Peripheral BDNF as a Potential Biomarker

As reduced BDNF is associated with several mental disorders, its role as a possible biomarker has been studied extensively (31). Several studies have shown that BDNF levels are decreased in mental disorders such as depression (40), schizophrenia (41, 42), anxiety disorders (43), and cognitive impairment (44), to name a few. According to Gass and Hellweg (31), one explanation could be that affective disorders share the common contributing and sustaining factor stress which is well known to influence BDNF levels, regulation, and signaling (45–48). One recent and rigorous review has proposed a BDNF stress-sensitivity hypothesis. The authors argue that disruption of endogenous BDNF activity by factors potentiates sensitivity to stress and vulnerability to stress-inducible illnesses and propose mechanisms by which BDNF may induce plasticity to promote fear and trauma while enabling adaptive plasticity during extinction learning (49). It is fair to conclude that alterations in BDNF levels are neither disease nor treatment specific since stress is a major factor in mental disorders. However, the differences observed in our study could partly be explained by smoking cessation being the altered factor in smokers, even though we were not able to control for all relevant confounding variables.

Limitations

The present study has several limitations. The reported BDNF levels could partly be explained by differences in BMI, since we could not perform an analysis of covariance. Nonetheless and of note, BMI did not correlate with BDNF plasma expression, suggesting that the differences found could be explained by smoking cessation. One explanation could be the relatively small sample size and the fact that we used non-parametric tests with lower power than parametric tests. Since we did not assess platelet count, we cannot perform further analysis to identify a possible influence of platelet count on BDNF expression levels and promoter methylation. In addition, we were only able to control for some of the previously mentioned confounding variables (Section Factors Influencing BDNF Expression).

Furthermore, we only investigated exon IV as being the most prevalent target in psychiatric research. While it is also worth noting that two studies reported opposing results, namely decreased BDNF levels in smokers, those studies also showed an increase of BDNF levels over 2–3 months (15). In contrast to these findings, we did not observe any convergence of BDNF levels with controls, supposedly due to the short observation period of 14 days of cessation. Since physical nicotine detoxification can last around 4 weeks and be associated with psychiatric side effects, it is essential to investigate BDNF levels and promoter methylation during a more extended follow-up period while correlating changes in methylation and plasma levels with psychometric parameters. In our study we put emphasis on those smokers that remained abstinent over the period of 14 days. Thus, we were not able to differentiate between abstainers and relapsers to analyze a possible role of BDNF as relapse marker, which should be done in future studies.

CONCLUSION

Our findings replicate those of previous studies that peripheral BDNF is elevated in smokers. Also, BDNF levels decreased during the short cessation period. Our novel findings of dysregulated methylation patterns in exon IV of the BDNF gene further support the hypothesis that epigenetic regulation of BDNF plays a role in nicotine dependence in a gender-dependent manner. Should further studies confirm these results, measuring BDNF promoter IV methylation to determine addiction severity and relapse probability could be a sensitive readout for the clinical application that could enhance therapy and indicate the efficacy of relapse prevention.

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 Ethics Committee, Medical School Hannover, 30625 Hannover. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG and MM planned and carried out the study. RL analyzed the BDNF ELISA measurements. VB and MR generated the methylation data. KA, PP, MD, and MR analyzed the data and wrote the manuscript. SB, BV, AG, MR, HF, KA, MM, PP, and MD critically revised and contributed to the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.897801/full#supplementary-material

Supplementary Figure S1 | Detailed CpG methylation for the analyzed promoter fragment of the BDNFIV exon. **(A)** Overview of mean methylation (*y*-axis) per CpG (*x*-axis) for Controls (blue) and patient timepoints (T0-green, T7-dark red, T14-bright red). **(B,C)** Provide the gender-specific display of all CpGs.As the general trend of the majority of CpGs is represented in the mean values for the whole fragment, we refrained from looking at a detailed comparison of certain positions for analysis. Error bars are ±1 SEM.

Supplementary Figure S2 | Comparison of methylation and protein levels with the Fagerström questionnaire results (FTND). **(A)** Nonparametric Spearman Correlation of Protein levels (BDNF_E), mean methylation (mean_meth), FTND and FTND binning for groups defined by Lesch et al. (>3 = 1, 3–4 = 2, >4 = 3, FTND Lesch). **(B)** Display of mean methylation values for the three Lesch FTND groups divided by timepoint (T0-green, T7-dark red, T14-bright red). **(C–H)** Plot of mean methylation **(C–E)** and protein levels **(F–H)** against the FTND questionnaire results. Regression means with R square values for total trend and according to sex are given for each timepoint.

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Oral Morphine as an Alternative Substitution Treatment for Opioid Use Disorder, a Rare but Non-risk-free Use

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Background: National health monitoring agencies have reported the alternative use of morphine sulfate painkiller for maintenance treatment of opioid use disorder (OUD), associated with a potential increase in overdose risk.

Objectives: This study sought to assess the prevalence of regular and occasional legally prescribed morphine use in patients treated for OUD and compare their characteristics to those of patients receiving conventional opioid maintenance treatment (OMT), buprenorphine or methadone. Then, we assessed the factors associated with opioid overdose risk.

Methods: Data were extracted from the French national healthcare system database, covering the entire population in 2015. Diagnosis associated with hospital discharge and long-term disease codes were extracted to select the population and identify outcomes and covariates. OUD non-chronic pain patients were divided into regular (≤35 days between dispensing and ≥3 months of continuous treatment duration) morphine users, and occasional users. Their sociodemographic and health characteristics were compared to OMT controls. A multivariate logistic regression model was performed to determine factors associated with opioid overdose.

Results: In patients treated for OUD, 2,237 (2.2%) morphine users (1,288 regular and 949 occasional), 64,578 (63.7%) buprenorphine and 34,638 (34.1%) methadone controls were included. The prevalence of regular morphine use among patients treated for OUD regularly receiving an opioid was 1.3%. Compared to users who receive morphine regularly, occasional users had an increased risk of overdose [OR = 2.2 (1.5–3.3)], while the risk was reduced in the buprenorphine group [OR = 0.5 (0.4–0.7)] and not significantly different for methadone [OR = 1.0 (0.7–1.4)]. Other overdose risk factors were low-income, comorbidity, i.e., psychiatric conditions, alcohol use disorder or complications related to intravenous drug use, and coprescription with benzodiazepines or pregabalin. These factors were more frequent in morphine groups.

Conclusions: Patients that were prescribed oral morphine represented a small minority of the treated for OUD. The poorer health condition affected by numerous comorbidities and higher risk of opioid overdose in patients treated with oral morphine compared with OMT controls points toward the need to better supervise the practices of these patients, to strengthen multidisciplinary care and risk reduction measures.

Keywords: opioid, morphine, substance use disorder, overdose, opioid maintenance treatment, healthcare database, morphine dependence, prescription medication misuse

INTRODUCTION

Problematic prescription opioid use is a reality for many industrialized countries (1–8) and French national pharmacosurveillance systems have reported the diversion of a specific slow-release pharmaceutical product containing morphine sulfate (MS), named Skenan®. This analgesic is available in capsule form, dosed at 10, 30, 60, 100, and 200 mg. It is these lats two highest doses (100 and 200 mg) that are particularly diverted, as confirmed by field studies (9–13). This analgesic is diverted by a minority of patients, sometimes as an occasional illicit drug replacement for heroin, or more regularly in agreement with the prescribing physician, as an alternative opioid maintenance therapy (OMT).

In France, only two medications, buprenorphine and methadone, are approved for the treatment of opioid use disorder (OUD), while MS is only validated as a painkiller. Buprenorphine and morphine can be prescribed by any physician, while methadone can only be prescribed by an addiction specialist. There is currently no real legal framework for the prescription of morphine as an alternative to OMT, which can be prescribed by any physician, regardless of his or her specialty and without restriction regarding the context of care (private practice, primary care, addiction center, or other), nor are there any eligibility criteria well-defined for this treatment. Prescribing MS as an alternative OMT may be justified when the patient reports intolerance or ineffectiveness of conventional OMT (14). This care framework must be identical to that of conventional OMT, with regular medical prescriptions and dispensing in pharmacies. Heroin-alternative MS users report greater availability and quality consistency compared to heroin fluctuations (15). The misused MS then comes either from sporadic medical prescriptions dispensed in pharmacies or from the illicit-market (9–11).

In addition to risks linked to opioid use, notably overdose, there are also those associated with the route of administration. Either as a substitute or alternative to heroin, the MS oral formulation is usually crushed and dissolved to be injected intravenously (10, 11). The alteration of the oral galenic to make it injectable induces risks of thrombosis due to the defective filtration of certain excipients, while the intravenous route presents risks of bacterial and viral complications, both local and systemic (16–22).

A retrospective pharmacoepidemiological study was performed to assess the use of MS prescribed as an alternative OST in patients with OUD and without any chronic pain. The primary study objective was to assess the prevalence of regular and occasional MS use in patients with OUD. The secondary objectives were (i) to compare sociodemographic and health characteristics in patients with OUD treated using MS or conventional OMT, and (ii) to determine the associated factors of opioid overdose.

MATERIALS AND METHODS

Study Design and Data Source

This retrospective descriptive study included patients receiving oral MS, buprenorphine, or methadone in OUD context. It conformed to the RECORD-Pharmacoepidemiological recommendations (23–26).

Data were extracted from the French national healthcare system data (SNDS), often used for public health and pharmacoepidemiological research, between 01/01/2015 and 12/31/2015. SNDS covers 98.8% of the population, comprising exhaustive anonymous individual administrative, medical, and pharmacy data (27, 28). Anonymous identifiers link health reimbursement data, diagnoses codes from hospitalization discharge databases using the 10th revision of the international statistical classification of diseases (ICD-10), and the death registry. Administrative data provides sociodemographic information: year of birth, sex, date of death, free complementary medical cover (CMUc) for low-income status, and any recognized chronic conditions from the list of 30 long-term/major diseases (LTD-30) that are guaranteed full reimbursement for any medical fees. This list is reviewed annually by the government and includes diseases that require particularly costly medical treatment for at least 6 months, like cancer, diabetes, severe heart disorder, chronic psychiatric, neurological or muscular diseases, and chronic lung disease, etc. (29). Pharmacy data comprise anonymous pharmacy identifiers and exhaustive claims for all reimbursed medications dispensed in pharmacies (substances and quantities supplied, dates of prescription, and dispensing) including opioid medications,

Abbreviations: aOR, Adjusted odd ratio; ATC, Anatomical therapeutic chemical; CCI, Charlson comorbidity index; CI, Confidence interval; CMUc, Free complementary medical cover; CNIL, French national data protection commission; DSB, Doctor shopping behavior; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; ICD-10, International statistical classification of diseases-10th revision; INDS, French institute for health data privacy; IQR, Interquartile range; LTD, Long-term/major diseases; MS, Morphine sulfate; OMT, Opioid maintenance treatment; OR, Odd ratio; OUD, Opioid use disorder; SD, Standard deviation; SNDS, French national system of health data.

enabling the daily dosage given to regular users to be estimated. Medical data comprise anonymous doctor identifiers and the specialty of the prescribers.

This study was approved for medical research by the French institute for health data privacy (INDS, no. 176) and the French national data protection commission (CNIL, no. 1946535). French law prohibits the authors from directly sharing the data used for this study, but access can be requested directly from SNDS (website: https://www.health-data-hub.fr).

Study Population

The criteria used for patient selection were validated by a previous study (30). In accordance with OMT prescription recommendations, we included all men and women aged 15 years and over to whom MS, buprenorphine or methadone was dispensed at least once in 2015. Patients who received regular and concomitant OMT and MS prescriptions were excluded from the analysis due to the inability to link potential complications to either of the two opioids.

OUD patients were identified as:

- having been dispensed buprenorphine or methadone at least once in 2015;
- on the basis of hospital discharge reports or chronic conditions for OUD ICD-10 codes.

All patients diagnosed with cancer or receiving palliative care, as well as patients with chronic pain, were excluded. Patients with chronic pain were identified based on:

- specific ICD-10 codes from hospital discharge reports or LTDs for chronic pain or rheumatic disorders for which MS is recommended in France (31);
- identification of care given in pain clinics;
- identification of continuous analgesic prescription, other than MS, for at least 3 months, considered as the management of chronic pain (32);
- non-affiliation to 'diagnosis-related groups' who have undergone surgery, to exclude patients who have received MS for post-operative pain.

All ICD-10 codes applied to select the patients are outlined in **Supplementary Table 1**.

Medications Exposure

Medications were identified by their Anatomical Therapeutic Chemical (ATC) codes ("N02AA01" and "N02AA51" for morphine alone and in combination, respectively, "N07BC01" for buprenorphine, and "N07BC02" for methadone). Dates of dispensings were used to determine frequency of use.

For MS, buprenorphine and methadone "capsule," regularity was defined as receiving the medication over at least three consecutive months, during which the treatment was regularly dispensed, i.e., with <35 days between each pharmacy dispensing. This 35-day threshold corresponds to French legal restrictions on opioid medications, which limit their prescription and dispensing to a maximum of 28 days, to which a grace period of 7 days was added in order to avoid overestimating medication discontinuation. Methadone 'syrup' is subject to stricter legislation, with a maximum dispensing period of 14 days, making it necessary to adapt the regularity criterion to 18 days (14 days, plus 4 days of grace period). Patients who fulfilled these criteria were considered regular medication users.

Four groups have been formed. The first comprised all patients with regular MS use in OUD context in 2015. Those who did not fulfill these MS regular-user criteria, but received at least two MS doses in 2015 were included in the second group. The last two groups comprised all OUD control patients receiving regular OMT, separated into buprenorphine on one hand and methadone on the other.

Study Outcomes and Covariates

All administrative, medical and pharmaceutical data mentioned in "data source" were extracted. All ICD-10 codes applied to identify outcomes and covariates are outlined in **Supplementary Table 1**.

Diagnosis associated with hospital discharge were extracted to identify unintentional opioid overdoses.

In the same way, diagnosis associated with hospital discharge and LTD codes were extracted to identify the covariates: human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and the main infection complications described as potentially related to intravenous drug injection (16–19). Arterial and venous thrombosis complications (20–22) and various data on comorbidities: severe chronic psychiatric disorders (LTD-23), alcohol use disorders (by ICD-10 code and specific treatments (33), [i.e., disulfiram ("N07BB01"), acamprosate ("N07BB03"), naltrexone ("N07BB04"), and nalmefene ("N07BB05")], benzodiazepine [anxiolytics ("N05BA") and hypnotics ("N05CD," "N05CF")], and gabapentinoids [pregabalin ("N03AX16") and gabapentin ("N03AX12")]) concomitant treatments were also collected. Coprescription was defined as receiving dispensings of the medications involved on exactly the same date, suggesting that the treatments were simultaneously on the same prescription.

Doctor shopping behavior (DSB) was measured in regular morphine, buprenorphine and methadone groups. DSB was defined as a combination of overlapping prescriptions for a specific medication from several different prescribers, dispensed in different pharmacies, to the same patient. This practice enables patients to increase the amount of medications they receive (34, 35) and is typically associated with high levels of misuse and/or diversion (36–40). In this study, the threshold defining a DSB was fixed as:

- at least one day of overlapping prescriptions;
- and at least two different prescribing physicians;
- and at least three different dispensing pharmacies during the study period.

These thresholds correspond to those established by previous studies assessing DSB scores for opioid analgesics, ensuring the comparability of results (41, 42). DSB is measurable only for regular substance use and so is not applicable to the occasional MS group.

The daily opioid dose was calculated for the three regular groups of patients and its oral morphine equivalent was evaluated

with a fixed 30:1 ratio for buprenorphine (43) and a validated variable ratio ranging from 4:1 to 12:1 based on the daily dose for methadone (44).

The Charlson Comorbidity Index (CCI), extensively applied in clinical research to account for the confounding influence of comorbidities was calculated (45–47). The CCI assesses the level of comorbidity by considering the level of severity of 19 predefined comorbid disorders, as well as the number of disorders present among them by means of a score (48).

Statistical Analyses

Categorical variables were expressed as frequencies and associated percentages, and quantitative variables as mean ± standard deviation (SD) or median and interquartile range (IQR), according to their statistical distribution (normality assessed using the Shapiro-Wilk test). The comparison between groups was performed using the chi-squared test for categorical data or Fisher's test where appropriate, with a variance analysis for continuous variables or the Kruskal-Wallis test if normality was rejected.

To determine the influence of various factors associated with overdose in opioid patients, a univariate logistic regression model was performed. The associated p-values were computed with their corresponding odds ratios (ORs) and their 95% confidence intervals (95% CI). To study the factors associated with opioid overdose, a multivariate logistic regression analysis was performed. All variables associated with $p < 0.25$ in univariate analysis were included in the model. Age and sex were forced in the model. The corresponding adjusted ORs were calculated with their 95% CIs. All statistical analyses were conducted using SAS-9.4 software (SAS Institute, USA) and STATA-14.2 (StataCorp, USA).

RESULTS

Population Description

From 1 January to 31 December 2015, 101,453 patients with OUD were included, among whom 2,237 patients receiving MS in the context of OUD (2.2%). MS groups were divided between the 1,288 patients who regularly received MS (1.3%), and the 949 who received it occasionally (0.9%) (see flow chart, **Figure 1**).

A total of 99,216 OMT controls were included in the same period, with 64,578 (63.7%) patients treated with buprenorphine, and 34,638 (34.1%) with methadone (see **Supplementary Figure 1**). Of the 100,504 OUD patients regularly receiving a regular opioid substitution (MS, buprenorphine or methadone), 1.3% ($n = 1,288$) were regular prescribed MS users.

The study population is described in **Table 1**. Mean ages were similar in MS and buprenorphine groups; methadone control patients were younger. All groups displayed the same sex ratio, four men to one woman. Over a third of patients receiving MS were considered low-income, based on their CMUc status. The poverty level was higher in regular MS users than occasional ones ($p < 0.01$), and overall, it was higher in MS groups than controls ($p < 0.01$) of which only a quarter benefited from CMUc.

MS users presented the highest prevalence of psychiatric disorders, with similar rates in both regular and occasional users ($p = 0.1$). Alcohol use disorder was more frequent for occasional than regular MS users ($p < 0.01$) and controls. Control groups were not different ($p = 0.15$). Regular MS users received benzodiazepines coprescriptions more frequently, with rates similar in other groups. Gabapentinoids coprescription rates were higher in MS users than in control groups, which were comparable between them ($p = 0.5$). Regular MS users received gabapentinoids more frequently (pregabalin and/or gabapentin) coprescriptions than occasional ones ($p = 0.01$).

Outcomes

There were significant differences across all MS patients and OMT control groups ($p < 0.01$) in terms of the prevalence of overdose. Occasional MS patients presented the highest prevalence, followed by regular MS users ($p < 0.01$). The controls were less affected, particularly those taking buprenorphine compared to methadone ($p < 0.01$). Compared to controls (no difference between buprenorphine and methadone, $p = 0.88$), the mortality rate was higher in MS users ($p < 0.01$), and significantly higher for occasional MS users than regular ones ($p < 0.01$).

DSB were significantly higher in regular MS users compared to controls ($p < 0.01$). Buprenorphine controls exhibited significantly higher DSB prevalence than methadone controls ($p < 0.01$).

Compared to OMT controls, between which no difference was found ($p \geq 0.1$), the prevalences of HIV and HBV infections were significantly higher in MS users, although there was no difference between the regular and occasional groups ($p \geq 0.1$). It is noteworthy that only the prevalence of HCV infection was different ($p < 0.01$) across all groups, as it was higher among MS (regular > occasional) users compared to controls (methadone > buprenorphine) ($p < 0.01$). The prevalence of bacterial infections was 3.5 times higher in MS groups, $p < 0.01$, with no difference between regular and occasional MS users, $p = 0.62$. The prevalence of thrombotic complications was higher in MS groups than in controls ($p < 0.01$), with comparable prevalence in occasional and regular MS users ($p = 0.3$).

Characteristics of MS and OMT Prescriptions

The pharmaceutical product Skenan®, a sustained-release MS capsule, was ahead of the other prescribed MS forms featuring on 91.3 and 86.9% of prescriptions dispensed to regular and occasional MS users, respectively. The pharmaceutical product Actiskenan®, an immediate-release morphine capsule, was the second most frequent MS dispensed to patients with OUD, featuring on 18.8 and 31.5% of prescriptions to regular and occasional MS users, respectively. The pharmaceutical product Moscontin®, an extended-release pill, came in third position, featuring in 5.2 and 2.7% of prescriptions dispensed to regular and occasional MS users, respectively (see **Supplementary Table 2**).

Analysis of Skenan® prescriptions showed a preference for the highest unit doses among regular users, less so

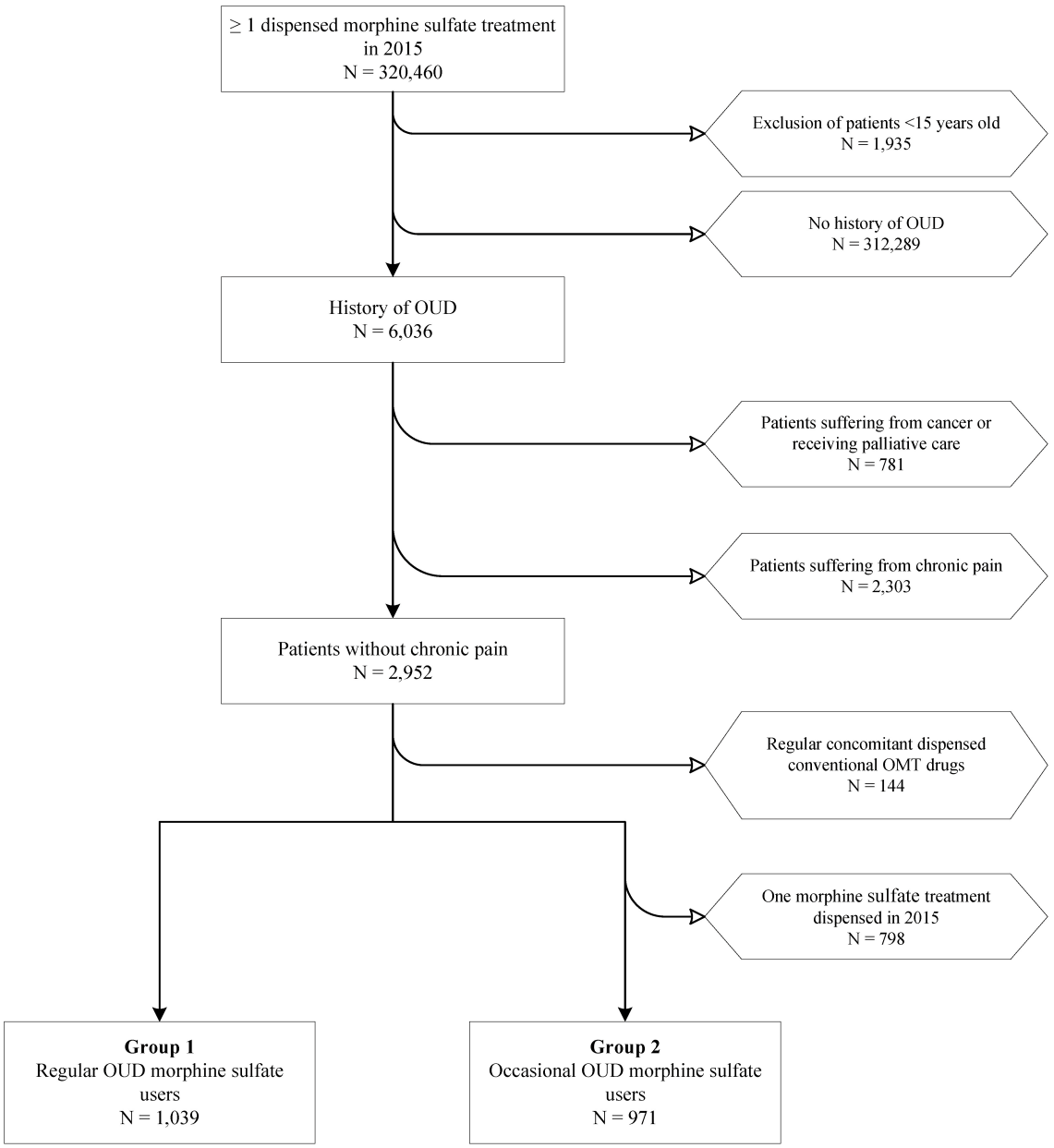

FIGURE 1 | Flow chart of patient selection for interest groups. OUD, opioid use disorder; OMT, opioid maintenance treatment.

among occasional users. For Actiskenan®, the dose distribution was more evenly distributed for regular users and low doses were more frequent in the occasional user group (see **Supplementary Table 2**). Regular MS users presented a median daily dose of 443.1 mg/day [IQR (192.8–758.4)], vs. 8.0 mg/day [IQR (4.1–14.5)] for buprenorphine-treated controls and 47.7 mg/day [IQR (28.9–71.8)] for those on methadone, corresponding to 240.7 mg/day [IQR (122.2–435.1)] and 286.3 mg/day [IQR (173.5–574.2)] equivalent oral morphine, respectively (**Table 1**).

The prescriptions mainly came from private practice medicine at similar rates among MS patients (regular: 87.4% of prescriptions, occasional: 85.4%) and buprenorphine controls (86.8%), slightly less for methadone controls (67.8%), mainly from general practitioners (GPs) for MS patients (regular: 97.8%, occasional: 97.7%) and similar in control groups (buprenorphine: 98.5%, methadone: 98.1%). Psychiatrists were the second main prescribers, accounting for <1.8% of prescriptions in each group. Occasional MS users more frequently received punctual conventional OMT prescriptions

TABLE 1 | Characteristics of patients included in the morphine sulfate and control groups.

	Regular morphine sulfate users with OUD history	Occasional morphine sulfate users with OUD history	Regular buprenorphine users with OUD history	Regular methadone users with OUD history	*P*-value
Number	*N* = 1,288	*N* = 949	*N* = 64,578	*N* = 34,638	
Mean age, years ± SD	40.5 ± 10.6	39.8 ± 11.0	39.9 ± 8.7	37.4 ± 8.2	<0.0001
Male sex, % (*N*)	74.8 (963)	78.4 (744)	79.7 (51,480)	76.1 (26,353)	<0.0001
Low-Income status (CMUc), % (*N*)	41.3 (532)	36.0 (342)	27.4 (17,704)	25.5 (8,825)	<0.0001
Overdose, % (*N*)	3.7 (48)	6.9 (65)	1.0 (664)	2.3 (780)	<0.0001
Death, % (*N*)	0.3 (4)	0.7 (7)	0.1 (43)	0.1 (24)	<0.0001
Doctor shopping behavior, % (*N*)	19.9 (256)		3.7 (2,369)	0.8 (280)	
History of HIV, % (*N*)	4.5 (58)	3.8 (36)	1.6 (1045)	1.8 (610)	<0.0001
History of HBV, % (*N*)	1.6 (21)	1.8 (17)	0.6 (396)	0.5 (173)	<0.0001
History of HCV, % (*N*)	27.4 (353)	20.3 (193)	12 (7,716)	12.7 (4,399)	<0.0001
Bacterial infection, % (*N*)	10.5 (135)	10.9 (103)	3.1 (1,995)	2.9 (1,018)	<0.0001
Thrombotic complication, % (*N*)	3.2 (41)	2.7 (26)	0.9 (584)	1.1 (374)	<0.0001
History of psychiatric disorder (LTD-23), % (*N*)	47.9 (617)	44.7 (424)	26.8 (17,301)	34.3 (11,893)	<0.0001
Alcohol use disorder, % (*N*)	25.8 (332)	32.5 (308)	17.8 (11,480)	18.1 (6,285)	<0.0001
Anxiolytic benzodiazepine coprescription, % (*N*)	53.2 (685)	38.9 (369)	37.1 (23,986)	35.5 (12,294)	<0.0001
Hypnotic benzodiazepine coprescription, % (*N*)	32.2 (415)	19.7 (187)	19.7 (12,741)	20.3 (7,013)	<0.0001
Benzodiazepine anxiolytic and hypnotic coprescription, % (*N*)	23.4 (301)	12.9 (122)	12.6 (8,165)	12.8 (4,423)	<0.0001
Pregabalin antiepileptic coprescription, % (*N*)	4.4 (56)	4.1 (39)	0.9 (570)	0.8 (275)	<0.0001
Gabapentin antiepileptic coprescription, % (*N*)	1.1 (14)	0.6 (6)	0.2 (120)	0.2 (58)	<0.0001
Both gabapentinoid coprescription (pregabalin and gabapentin), % (*N*)	0.2 (2)	0 (0)	0 (14)	0 (5)	<0.0001
Opioid daily dose, mg, median, [IQR]	443.1 [192.8–758.4]		8.0 [4.1–14.5]	47.7 [28.9–71.8]	
Oral morphine equivalent, mg median, [IQR]			240.7 [122.2–435.1]	286.3 [173.5–574.2]	
Coprescription, % (*N*)					
morphine sulfate + OMT ≥ 3 episodes	20.8 (268)	26.2 (249)			

OUD, opioid use disorder; SD, standard deviation; CMUc, Free complementary medical cover; HIV, Human immunodeficiency virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; LTD, Long-term/major diseases; IQR, Interquartile range; OMT, Opioid maintenance treatment.

(26.2%) alongside those of MS (≥3 prescriptions/year) than regular MS users (20.8%).

Factors Associated With Opioid Overdose

In univariate analysis (**Supplementary Table 3**), general characteristics associated with opioid overdose were young age ($p = 0.04$), low-income ($p < 0.01$), receiving morphine rather than a validated OMT, particularly in the case of occasional MS use ($p < 0.01$), receiving high oral morphine equivalent ($p < 0.01$), and having treatment misuse behaviors according to DSB ($p < 0.01$). Having multiple comorbidities (history of severe chronic psychiatric pathologies, alcohol use disorder and systemic infectious complications (**Supplementary Table 1**) described as potentially related to intravenous drug injection, arterial, and venous thrombosis complications or according to the CCI score) was significantly associated with opioid overdose risk in univariate analysis. Receiving concomitant benzodiazepines or gabapentinoids and opioid prescriptions was associated with overdose risk in univariate analysis ($p < 0.01$).

Opioid dose in oral morphine equivalent and shopping behavior, reflecting misuse of the medication, were removed from the final logistic regression model because they could not be assessed for occasional MS users.

In the multivariate model, compared to regular MS users, occasional MS users had an increased risk of overdose [aOR = 2.2 (1.5–3.3)], while the risk was reduced in the buprenorphine group [aOR = 0.5 (0.4–0.7)] and not significantly different for methadone [aOR = 1.0 (0.7–1.4)]. When buprenorphine was used as a reference, occasional MS users were at the highest risk of overdose [aOR = 4.5 (3.4–6.0)], followed by methadone controls [aOR =

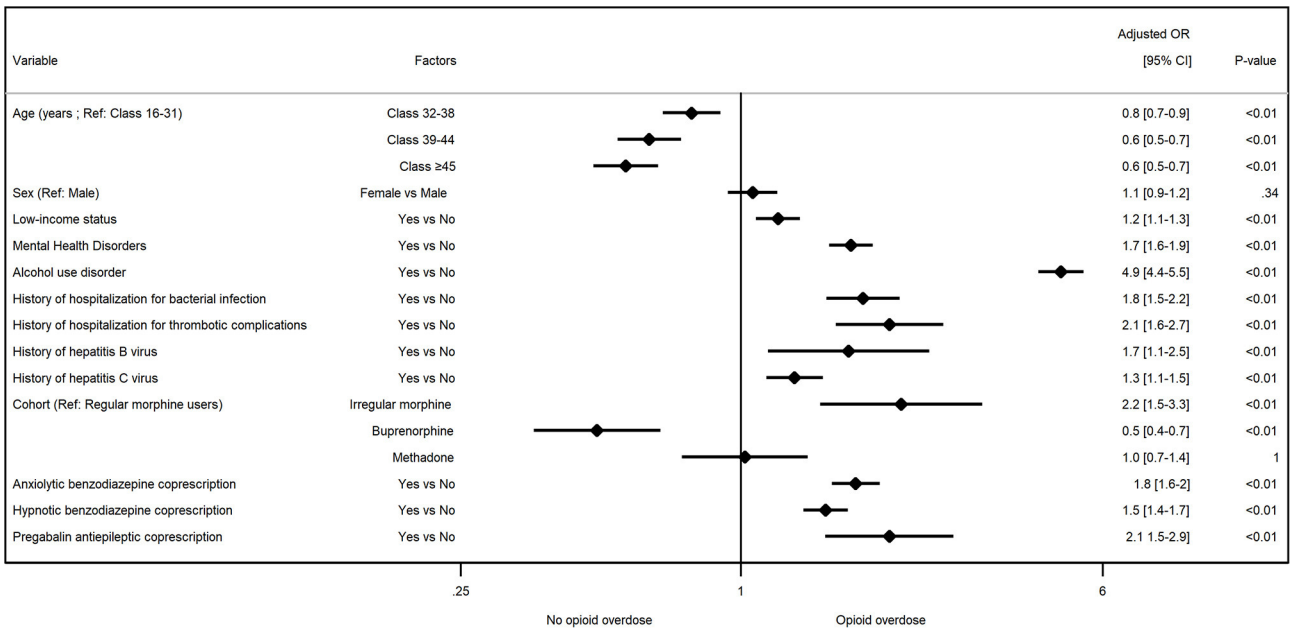

FIGURE 2 | Factors associated with opioid overdose in opioid use disorder patients in multivariate analysis. aOR, adjusted odd ratio.

2.1 (1.9–2.3)], and regular MS users [aOR = 2.0 (1.5–2.8)]. The graphical representation of the resulting multivariate logistic regression model corresponds to the forest plot in **Figure 2** (see also **Supplementary Table 4**). The area under the curve for multivariate model was equal to 0.822 ± 0.18 (**Supplementary Figure 2**).

Other factors associated with opioid overdose were age, with a risk decreasing over time regardless of the quartile evaluated ($p < 0.01$), being considered low-income [aOR = 1.1 95% CI (1.1–1.3), $p < 0.01$], history of mental health disorders [aOR = 1.7 (1.6–1.9), $p < 0.01$], alcohol use disorder [aOR = 4.9 (4.4–5.5), $p < 0.01$], infection complications described as potentially related to intravenous drug injection [aOR = 1.8 (1.5–2.2), $p < 0.01$], arterial and venous thrombosis complications [aOR = 2.1 (1.6–2.7), $p < 0.01$], HBV [aOR = 1.7 (1.1–2.5), $p < 0.01$], and HCV [aOR = 1.3 (1.1–1.5), $p < 0.01$]. Receiving concomitant benzodiazepines, anxiolytic [aOR = 1.8 (1.6–2.0), $p < 0.01$] or hypnotic [aOR = 1.5 (1.4–1.7), $p < 0.01$], or pregabalin [aOR = 2.1 (1.5–2.9), $p < 0.01$], and opioid prescriptions were associated with an increased overdose risk in multivariate analysis.

DISCUSSION

In France in 2015, 2,237 patients with OUD were dispensed MS, either regularly or occasionally, i.e., 2.2% of this population. Of the 100,504 patients regularly receiving regular opioid substitution (MS, buprenorphine or methadone) in OUD context, 1.3% (n = 1,288) were regular prescribed MS users.

The prevalence of overdoses was the highest in MS users compared to controls. The overdose risk was similar in regular MS users and methadone patients, but higher in these groups than in buprenorphine patients. Compared to buprenorphine controls, occasional MS users had a 4.5 higher risk of overdose, twice that of regular MS or methadone users. This finding seems to indicate that regular MS use, "like a regular conventional OMT," reduces overdose risk compared to occasional MS use. The known safer pharmacological profile of buprenorphine is also reflected in our results (49, 50).

Several explanations can be given as to why regular opioid use may be more protective against overdose than occasional use. Having regular prescriptions means having regular medical follow-up, allowing better general monitoring of users' health, as well as better management of their comorbidities, which are also overdose associated factors. This regular monitoring also promotes global care, with the adoption of a harm reduction approach associated with treatment.

Finally, having regular prescriptions reduces fluctuations in self-administered doses of opioids (prescribed and possibly illegal). Although they have only irregular dispensing, occasional users still suffer from OUD, implying the onset of a withdrawal syndrome in the absence of regular opioid use. It can therefore be assumed that occasional users continue to use illicit-market opioids in addition to those occasionally prescribed to them, with the variability of self-administered doses that this implies. The stability of self-administered doses may explain the lack of difference in the opioid overdose risk observed between regular MS users and methadone patients.

This risk reduction occurs in patients with regular MS or OMT dispensings despite more frequent gabapentinoid

and/or benzodiazepine coprescriptions, possibly for psychiatric comorbidity and/or alcohol use disorder (51–53) which, combined with opioids may increase respiratory depression and overdose risk (53, 54). Although the involvement of benzodiazepines, gabapentinoids, and alcohol in the occurrence of opioid overdose is well-described in the literature (54–58), the highly significant increase in this risk in our multivariate analysis (**Figure 2**) should attract the attention of practitioners.

All-cause mortality was low in all groups although higher in MS users, probably partially due to their increased overdose rates and the consequences of intravenous injections. In multivariate analysis, the absence of any difference between regular MS and methadone groups in terms of opioid overdose leads to the suspicion that injection behaviors have a significant influence on deaths among MS patients. Therefore, risk reduction measures linked to intravenous injections among these MS users should be reinforced to possibly reduce their risk of death.

Regarding opioid diversion, the regular MS users presented more than a five-fold higher DSB prevalence than controls taking buprenorphine, a substance highly associated with DSB in France (59). The low DSB in methadone controls was consistent with the literature, likely due to the strict monitoring rules imposed on its prescription and dispensing that limit diversion (49, 60). Previous studies have drawn links between DSB, overdose, and death (37, 38, 59, 61), which could partially explain the increased risks in regular MS patients. This high DSB score may show the nomadic nature of certain MS users, but also their difficulty in integrating into our sometimes restrictive care system.

The systemic viral infection rate of MS users (HBV, HCV) and the rate of hospitalization for bacterial infections was, respectively, twice as high and four times greater than those of controls. The prevalence of thrombotic complications in the MS group was also double that of controls, leading us to suspect deficient filtration of excipients when dissolving the oral form for injection (18, 20). These findings are in line with the diversion of oral forms previously described in field studies (9–11) and are linked to opioid overdose in multivariate analysis.

There were more psychiatric comorbidities in MS users, along with higher alcohol use disorder prevalence. The latter was more marked in occasional than in regular MS users. According to previous studies, this may be linked to their increased low-income status (62–67).

Such comorbidities must therefore be systematically investigated and managed in MS users by trained professionals experienced with these dual disorders so common among patients in addiction centers. Moreover, multivariate analysis indicates that these comorbidities, especially alcohol use disorder, are associated with an increase in overdose risk in patients with OUD, in accordance with the literature (68).

These results show that MS prescription for OUD concerns a minority of patients, but suggest that MS exposes them to multiple increased risks compared to conventional OMT. The implementation of a specific care, prescription and dispensing framework would reduce the risk of infection complications, preventing overdose and associated mortality. This care framework should be flexible, so as not to scare off patients with the least stable lifestyles, who are often nomadic, and who change their prescriber depending on their current location. The main objective is to promote a regular "conventional OMT-like" prescription of MS, which appears to involve less risk than occasional use. In the absence of direct access to an addiction center, it might be worthwhile to offer them graduated alternative care. The first level would begin with simply providing risk-reducing tools to involved GPs, or through collaboration with an addiction center. Secondly, MS users could be sent to the GP's addiction center partner to receive multidisciplinary care. Direct or indirect support through the GP for MS prescription by an addictology center would limit the risk of exposing colleagues to the difficulties of caring for these complex patients and would encourage their entry into the multidisciplinary care framework they require. This care setting would be suitable for the eventual provision of an injectable substitution, alone or in addition to a validated OST, whose effectiveness has been scientifically documented (69–71). In various countries (including Switzerland, Netherlands, Germany, Denmark, and Canada), the legal prescription of heroin-assisted treatment under strict supervision has indeed proven to be effective and well-tolerated (69, 72–74).

Results on daily doses (only possible for regular users) confirmed that large MS doses were being taken, in line with already published data (6, 7, 9–11, 75, 76), exceeding those for chronic pain management. This could be a marker of early substance usage disorder (31), which should be a warning sign for prescribers. However, these high dosages are similar to those reported in clinical trials assessing the use of MS as an alternative OMT (77–83). Improving the training of physicians in the identification of OUD and proper prescription rules would promote early detection of these patients and safer use of opioids.

Strengths and Limitations

These findings should be interpreted by taking into account the strengths and weaknesses inherent in all pharmacoepidemiological studies using healthcare databases. The main risk is that the population included does not resemble that typically encountered in clinical practice. The characteristics of the patients included and controls were similar between groups and consistent with previous field studies (age, sex ratio, low-income status), as were our findings on complications (viral and bacterial infections, DSB) and medication dosages (9–12, 30, 60). This similarity validates our patient selection, despite a selective methodology, and shows the lack of influence of the impossibility to include the 10% of patients receiving their OMT dispensing in an addiction center rather than in pharmacies (9, 10).

Regarding the data source, the SNDS database only provides diagnosis codes attributed on hospital discharge ($\geq$24 h), excluding care provided by emergency services, and we only had access to data on pharmacy dispensing, without details on illicit-market sales. These missing data minimize the size of the groups and the risks to which they are exposed. While our results add to the body of knowledge on opioid overdose and MS use, and are consistent with the results of a previous incidence study on the issue (30), a causal inference cannot be determined directly owing to the cross-sectional design of the study. Further longitudinal

studies are needed to explore the temporal relationship between the factors we have identified and opioid overdose. Although oral morphine use disorder seems to be rather specific to France, the main risk factors for opioid overdose do not seem to be specific to this population. The generalization of the study results beyond the French territory must be done with caution and conditioned on future investigations. However, these results may be of interest to countries exposed to the intravenous diversion of oral opioid medications or which wish to offer patients an injectable opioid substitution.

This study also presents significant strengths, notably its ability to recruit a large number of patients for assessing rare issues. This pharmacoepidemiologic approach using a nationwide database is alone in providing sufficient cohort sizes to supply reliable data at the population level, particularly for the patients described here, who are few in number and difficult to follow-up in conventional clinical studies.

CONCLUSION

This is the first pharmacoepidemiological study to report the prevalence of 1.3% off-label MS regular users in France among patients regularly receiving OMT for OUD. The high vulnerability and associated comorbidities of these MS users encourage their referral to addiction centers rather than to a GP, so that they can receive multidisciplinary care. Although MS prescription for OUD is considered relevant, it should be accompanied by information on overdose risks and the dispensing of emergency naloxone kits. To reduce the risks associated with the widespread practice of MS intravenous injection, these users should be systematically provided with free sterile injection kits, suitable for this practice, containing large-volume syringes, and special filtering tools (11, 84, 85). The availability of an injectable substitution opioid, self-administered under medical supervision, and ensuring better aseptic conditions, would make it possible to reduce the risks discussed above by promoting access to care for these complex patients.

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

CB, JD, CC, NA, and JB: conceptualization and methodology. CB and JD: software, data extraction, and formal analysis. CC, JB, and NA: validation and supervision. CB: writing of manuscript. CB, CC, NK, NA, MT, JB, and AP: revision of manuscript. NA: project administration and funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.893590/full#supplementary-material

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Right Inferior Frontal Activation During Alcohol-Specific Inhibition Increases With Craving and Predicts Drinking Outcome in Alcohol Use Disorder

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Alcohol use disorder (AUD) is characterized by enhanced cue-reactivity and the opposing control processes being insufficient. The ability to inhibit reactions to alcohol-related cues, alcohol-specific inhibition, is thus crucial to AUD; and trainings strengthening this ability might increase treatment outcome. The present study investigated whether neurophysiological correlates of alcohol-specific inhibition (I) vary with craving, (II) predict drinking outcome in AUD and (III) are modulated by alcohol-specific inhibition training. A total of 45 recently abstinent patients with AUD and 25 controls participated in this study. All participants underwent functional magnetic resonance imaging (fMRI) during a Go-NoGo task with alcohol-related as well as neutral conditions. Patients with AUD additionally participated in a double-blind RCT, where they were randomized to either an alcohol-specific inhibition training or an active control condition (non-specific inhibition training). After the training, patients participated in a second fMRI measurement where the Go-NoGo task was repeated. Percentage of days abstinent was assessed as drinking outcome 3 months after discharge from residential treatment. Whole brain analyses indicated that in the right inferior frontal gyrus (rIFG), activation related to alcohol-specific inhibition varied with craving and predicted drinking outcome at 3-months follow-up. This neurophysiological correlate of alcohol-specific inhibition was however not modulated by the training version. Our results suggest that enhanced rIFG activation during alcohol-specific (compared to neutral) inhibition (I) is needed to inhibit responses when craving is high and (II) fosters sustained abstinence in patients with AUD. As alcohol-specific rIFG activation was not affected by the training, future research might investigate whether potential training effects on neurophysiology are better detectable with other methodological approaches.

Keywords: alcohol use disorder (AUD), craving, drinking outcome, fMRI, Go-NoGo, inferior frontal gyrus (IFG), inhibition, inhibition training

INTRODUCTION

Alcohol use disorder (AUD) is a leading cause for societal and individual burden of disease (1, 2) and treatment still needs to be improved (3). Central to the disorder is the fact that patients with AUD repeatedly fail to inhibit or control their drinking and continue drug use despite negative consequences. Establishing an ability to resist drinking urges and inhibit drinking behavior is thus of major importance for AUD treatment. While multiple brain networks are implicated in AUD (4–6), two processes seem crucial when it comes to inhibition in an alcohol-related context. Neuroscientific models postulate that, on the one hand, cue reactivity and subjective craving in response to alcohol-related stimuli is too strong; On the other hand, control processes are too weak to inhibit resulting drinking urges (4, 6, 7). These models, as well as clinical experience, thus suggest that inhibitory control is especially relevant in the context of the opposing appetitive processes, making alcohol-specific inhibition particularly important for AUD.

On a behavioral level, patients with AUD displayed inhibitory deficits (8–10) when their performance on inhibitory control tasks such as the Go-NoGo (GNG) task and the stop signal task was compared against healthy control groups. These deficits were reported to be pronounced in an alcohol-related compared to a neutral context (11–14). On a neurophysiological level, response inhibition is typically supported by a right lateralized fronto-striatal-parietal network (15, 16), which seems to be dysregulated in AUD (4, 5, 17, 18). The response inhibition network includes dorsolateral and ventrolateral prefrontal cortices, medial frontal regions (pre-SMA and ACC), thalamus, dorsal striatum, and the inferior parietal lobe (18). While most of these areas are involved in a broad variety of cognitive control tasks, the right ventrolateral prefrontal cortex (IFG, particularly BA 44/45) seems to be crucial for response inhibition (19–21) and specifically activated by response inhibition tasks (22, 23).

Dysregulations in the inhibitory control network in AUD and other addictive disorders have been repeatedly observed (5, 17, 18) in prefrontal, parietal and cingulate regions as well as in basal ganglia (24–30). Inconsistencies regarding the direction of this dysregulation (hypo- or hyperactivation) have been attributed to differences in task design and analytic strategy (17), to the extent of performance deficits (5, 31) and to variations in the stimulus material used (4). When assessed with GNG or stop-signal-tasks, hyperactivation during inhibitory control has rather been reported when addiction-related stimuli are used (24, 29, 31) and/or no behavioral performance differences are observed (25, 26, 29, 31–34), while hypoactivation was rather observed in studies using neutral stimuli (30, 35–38) and/or also reporting performance deficits (35, 36). This might be indicative of a general impairment of the inhibitory system, which is hypo-activated and less responsive unless confronted with addiction-related cues and/or charged with functional compensation in order to achieve near-normal task performance (4, 5, 26, 31).

Following the logic that response inhibition is especially crucial in the context of alcohol-related cues, which may trigger strong appetitive processes (4, 39–41), some studies have investigated alcohol-specific inhibition. When brain activation during inhibition in an alcohol-related context is directly compared to neutral inhibition, AUD seems to be characterized by increased neural activation during alcohol-related inhibition (29, 31). Furthermore, this alcohol-specific inhibitory activation was observed to increase with craving (31, 42, 43), suggesting that alcohol-specific inhibition is especially effortful in subjects experiencing high craving. Moreover, two studies reported that electrophysiological correlates of alcohol-specific inhibition discriminated between patients which relapsed and those who remained abstinent in the following 3-month period (43, 44), hinting at the potential clinical relevance of this specific subtype of inhibition. A potential linkage between drinking outcomes and the functional neuroanatomy of alcohol-specific inhibition, as assessed with fMRI, has not yet been investigated.

Taken together, neuroscientific and experimental research in AUD suggests that inhibition is crucial, and probably also particularly difficult, when it must be exerted in an alcohol-related context which provokes craving.

Following a translational approach, such research led to the development of an alcohol-specific inhibition training (Alc-IT), which was designed to improve patients' inhibitory control over their responses to alcohol-related stimuli (45, 46). Alc-IT led to mixed, but nonetheless promising, results in a series of non-clinical proof-of-concept studies (3). Recently, a first clinical RCT tested its effects as an add-on to treatment as usual (47) and reported positive effects for an improved variant of Alc-IT. This improved Alc-IT operates like a modified GNG task with a high Go/NoGo-ratio and selectively pairs alcohol-related pictures with NoGo cues, while neutral pictures are paired with Go cues. Thus, it establishes a prepotent response tendency, which then must be inhibited in the context of alcohol-related stimuli. The precise working mechanism of improved Alc-IT is still being debated (3), one proposition holds that it works *via* the improvement of alcohol-specific inhibitory capacities. Such a working mechanism would potentially also induce changes in the neurophysiological correlates of alcohol-specific inhibition.

The presented study thus aims to (I) replicate earlier reports indicating that neuronal activation related to alcohol-specific inhibition increases with craving; (II) test whether neuronal activation related to alcohol-specific inhibition is related to drinking outcomes and (III) investigate whether the neurophysiological signature of alcohol-specific inhibition can be altered through alcohol-specific inhibition training.

MATERIALS AND METHODS

Procedure

In the context of a randomized-controlled, double-blind, clinical trial investigating the effects of alcohol-specific inhibition training on drinking outcomes (47), the present paper reports on an additional sub-study, which investigated the neuronal correlates of the improved version of this inhibition training. For this sub-study, 49 patients were recruited to participate in a longitudinal multimodal MRI-study. Only fMRI data were included in the present analyses and are described in detail. All patients were recruited at the beginning of their residential treatment program. During the second treatment week, a

baseline measurement comprised questionnaires, diagnostics, and a Timeline-Follow-Back interview (TLFB). About one to two weeks later, a pre-training assessment comprised questionnaires and a multimodal MRI measurement, which also comprised fMRI measurement during participation in a GNG task. An independent investigator then randomly assigned the patients to one of two computerized training interventions using block randomization with variable block sizes [stratified according to gender and age (age groups: 18–25, 26–35, 36–45, 46–55, and 56–60)] following a randomization list generated with MATLAB (version 2017a, Mathworks, Natick, USA). The list was stored in a locked place; thus keeping participants, care providers, investigators and members of the study team blind to the allocation. During treatment weeks 4 and 5, all patients participated in six short (∼10–15 min) training sessions of their allocated condition (improved Alc-IT, or control training). The patients' average reaction times and error rates were communicated after each training session to maintain motivation. Between 1 and 4 days after the last training session, a post-training assessment comprised the same measures as the pre-training assessment, including the fMRI session. Patients were then to complete their residential treatment (∼8–12 weeks in total). Upon discharge from residential treatment, a questionnaire battery was administered. Three months after discharge from treatment, all patients were contacted by mail and by telephone and primary outcome variables for the 3-month follow-up were assessed in a short telephone interview, a TLFB interview, and a questionnaire battery. See Tschuemperlin et al. (47) for detailed study protocol of the main study.

Participants

All 49 patients were attending a 12-week abstinence-oriented residential treatment program for AUD in a specialized treatment center in Switzerland (Clinic Suedhang). Inclusion criteria were 18–61 years of age, main diagnosis of AUD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5; (48)], right-handedness and abstinence from alcohol for at least 4 weeks prior to MRI measurement. Exclusion criteria were other severe substance use disorders [except nicotine; Drug Use Identification Test DUDIT $\geq$25 per substance, (49)], current medical conditions preventing participation (e.g., acute infectious disease), diagnosed neurocognitive disorders (e.g., Korsakoff syndrome), contraindications to perform an MRI or inability to read and understand the participant's information. A control group was recruited including 27 right-handed healthy adults. Low scores of psychopathology [Brief Symptom Check List, BSCL (50, 51) $GSI_{t-value} \leq 63$] as well as non-problematic drinking behavior [Alcohol Use Disorders Identification Tests, AUDIT (52) < 8; Alcohol Use Disorder Scale, AUD-S (53) < 2] were inclusion criteria. Exclusion criteria were current or past substance use or disorder [Drug Use Disorders Identification Test, DUDIT (54) < 8 per substance, except nicotine], current psychiatric diagnosis or treatment, and other neurocognitive complications. All participants provided written informed consent and received a reimbursement of 50 Swiss Francs for participation. The main study was approved by the local ethics committee (KEK-number: 2016-00988) and registered at ClinicalTrials.gov (NCT02968537) and the Swiss National Clinical Trials Portal (SNCTP000002043). For more details on procedure, tasks, materials, and questionnaires used in the main study, see Tschuemperlin et al. (47). Three patients discontinued before the first MRI measurement and one had to be excluded because of technical problems during fMRI measurement scan, leading to a final analytic sample of $N = 45$ patients and $N = 25$ healthy controls for the analysis on alcohol-specific inhibition. See **Figure 1** for an overview of analytic sample sizes for the different analyses. Detailed sample description is shown in **Table 1**.

Questionnaires and Interviews

At baseline, a trained study member verified AUD diagnosis with the Diagnostic Expert System for Psychiatric Disorders [DIA-X, the AUD part adapted to DSM-5, (55)]. A questionnaire battery assessed self-rated AUD symptoms [Alcohol Use Disorder-Scale, AUD-S, adapted to DSM-5, (53)], alcohol-related problems [Alcohol Use Disorders Identification Tests, AUDIT (52)], general psychopathological symptoms [Brief Symptom Check List, BSCL (50, 51)], depressivity [Beck Depression Inventory, BDI-II (56)], anxiety [Beck Anxiety Inventory, BAI (57)] alongside demographics, socioeconomical data and other relevant clinical characteristics [see Tschuemperlin et al. (47)] for a complete description of measures. Also included in this questionnaire battery was the Obsessive Compulsive Drinking Scale [OCDS-G (58)], which assessed transsituational craving in the prior week. The OCDS is a reliable and widely used measure of transsituational craving that has been validated in populations similar to the current sample (58–61). Next to an overall score and a cognitive subscale, the OCDS provides a subscale capturing the behavioral aspects of craving such as drinking compulsions. This subscale (OCDSimp) has been used in prior similar studies and is also used here to operationalize craving in order to allow for optimal comparability and integration of the present study in literature.

Assessment of alcohol consumption was assessed at baseline (assessing drinking in the 90 days prior to detoxification entry) and 3-month follow-up (assessing drinking in the 90 days following treatment discharge) with the TLFB interview (62). From TLFB data the percentage of days abstinent (PDA) was computed for baseline and 3-months follow-up after correction for days spent in a protected environment (i.e., a residential treatment center or a somatic hospital). The change in PDA [PDA Δ, computed as $PDA_{(3-monthfollowup)} - PDA_{(Baseline)}$] was used in those fMRI analyses, which investigated the relation between the neurophysiology of alcohol-specific inhibition and drinking outcomes.

Go-NoGo (GNG) Event-Related fMRI Task

The task used in this study to assess BOLD-responses of alcohol-specific and neutral inhibition was equal to the task in Batschelet et al. (43). Building on a classical, neutral Go-NoGo task (36, 63), this task was developed to investigate response inhibition in a neutral as well as in an alcohol-related context (see **Figure 2**). Participants were presented with a series of

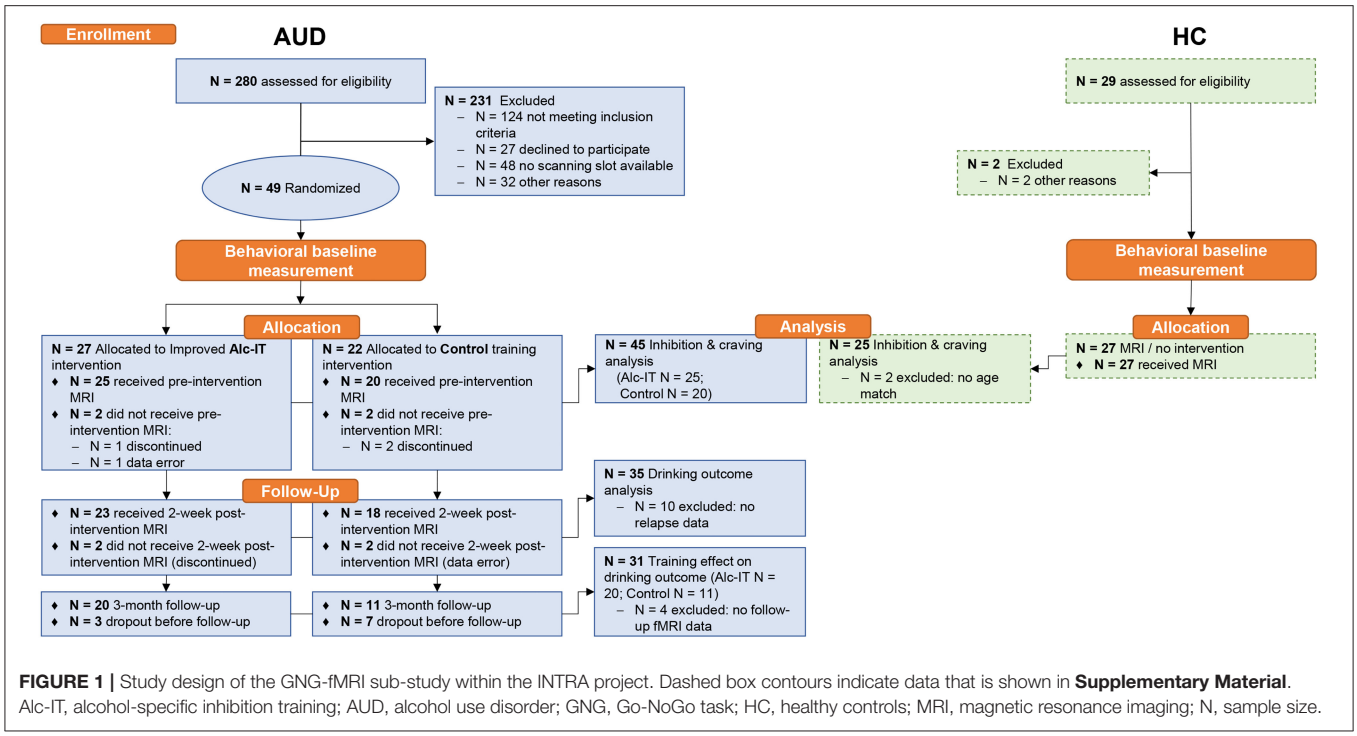

FIGURE 1 | Study design of the GNG-fMRI sub-study within the INTRA project. Dashed box contours indicate data that is shown in **Supplementary Material**. Alc-IT, alcohol-specific inhibition training; AUD, alcohol use disorder; GNG, Go-NoGo task; HC, healthy controls; MRI, magnetic resonance imaging; N, sample size.

TABLE 1 | Descriptive statistics and clinical scores stratified by study groups.

	AUD Alc-IT ($n = 25$)	AUD Control ($n = 20$)	HC ($n = 25$)	
	Mean (std. dev.)	Mean (std. dev.)	Mean (std. dev.)	*p*
Age, years	43.6 (10.4)	43.1 (8.2)	37.4 (12.7)	0.13
Gender (F/M)	9/16	7/13	11/14	–
Education, years	14.5 (3.7)	13.3 (3.1)	16.4 (3.1)[a]	0.004**
Employment, yes/no	12/13	12/8	23/2	–
Smoking tobacco, yes/no	18/7	12/8	–	–
Nr. of detox	3.0 (3.0)[b]	3.2 (2.9)[c]	–	1.0
Years of probl. drinking	13.3 (14.1)[f]	11.9 (9.7)[g]	–	0.88
AUDIT	24.6 (6.9)	24.9 (7.5)	–	0.91
BSCL GSI	1.3 (0.8)	1.1 (0.6)	0.17 (0.17)	<0.001***
BDI II	14.8 (10.3)[h]	16.7 (9.9)[i]	–	0.67
BAI	8.5 (11.5)	9.1 (7.8)	–	0.91
OCDSimp	13.8 (3.5)	14.1 (3.7)	1.9 (1.8)	<0.001***
OCDScog	10.0 (4.7)	9.8 (5.1)	0.1 (0.3)	<0.001***
OCDSsum	23.8 (7.5)	23.9 (8.1)	2.0 (1.9)	<0.001***
PDA Δ	72.5 (20.8)[d]	56.1 (45.9)[e]	–	0.28
AUD-S	28.1 (7.5)	30.0 (7.9)	–	0.49

[a]$n = 24$, [b]$n = 12$, [c]$n = 11$, [d]$n = 22$, [e]$n = 15$, [f]$n = 19$, [g]$n = 17$, [h]$n = 23$, [i]$n = 20$.

**$p < 0.01$; ***$p < 0.001$.

Alc-IT, alcohol-specific inhibition training; AUDIT, Alcohol Use Disorder Identification Test; AUD-S, Alcohol use disorder - Scale, BSCL-GSI, general symptom index of the Brief Symptom checklist; Control, Control training; F, Female; HC, healthy controls; M, Male; Nr. of detox, Number of prior detoxifications; OCDS, Obsessive-Compulsive Drinking scale. OCDSimp: subscale capturing compulsive drinking; OCDScog: subscale capturing cognitive aspects of craving; OCDSsum: overall score of transsituational craving; PDA Δ, Difference in Percentage of days abstinent between baseline and 3-months follow-up; std. dev., standard deviation; TTFD, Time to first drink in days after discharge from inpatient treatment; 3m-FU, Assessment 3 months after discharge from inpatient treatment; WHOQOL, WHO Quality of Life Scale (47).

pictures on a computer screen and were instructed to press a button as soon as possible whenever the presented picture changed (Go trial), but to withhold that response, when the same picture was repeated (NoGo trial). Participants were instructed to answer as fast and as accurately as possible. Stimuli were tailored according to the personal preference of the participants by drawing from three sets of stimulus material (beer, spirits, or wine). Each set consisted of eight photographs of alcoholic (ALC) drinks and eight photographs of neutral (NEU) drinks (mineral water). All pictures were taken with a high-resolution camera in standardized lighting conditions (47). Each photograph was displayed 60 times to the participant, 52 times in a Go condition, and eight times in a NoGo condition. This sums up to 960 trials, comprising 416 Go_{ALC}, 416 Go_{NEU}, 64 $NoGo_{ALC}$, and 64 $NoGo_{NEU}$ trials, leading to a Go/NoGo ratio of 6.5. The trials were presented in a pseudorandomized order with a mean of 7.5 Go-trials (i.e., 7.5 s) between two NoGo-trials. The task was subdivided into two blocks with a break of 1 min and 1 s. Photographs were displayed for 900 ms with a 100 ms inter-stimulus interval blank screen. The GNG-task was created and response data was logged with the E-Prime 2.0 software (Psychology Software Tools Inc., Pittsburgh, PA, USA).

MRI Data Acquisition

Functional and anatomical MRI data acquisition was conducted at the University Hospital of Bern, using a Siemens Magnetom Prisma scanner with 3 Tesla magnetic field strength and a head coil with 64 channels. For functional image acquisition during the above described GNG-task, a multi-band echo planar imaging (EPI) sequence was run (TR/TE = 1,300/37 ms; 60 slices; slice thickness = 2.2 mm; voxel-size 2.2 × 2.2 × 2.2 mm; FOV = 230 × 230 mm; matrix size = 105 × 105). For subsequent image distortion correction, a b0 protocol was run to acquire 4 field map images (2 phase/amplitude each) with the same image geometry as in the EPI-sequence, with TR/TE1/TE2 = 591/4.92/7.38 ms. Anatomical images were obtained using an MP2RAGE sequence (TR/TE = 5,000/2.98 ms; inversion time T1/T2 = 700/2,500 ms; 256 slices; slice thickness = 1.0 mm; voxel-size 1 × 1 × 1 mm; FOV = 256 × 256 mm; matrix size = 256 × 256). Note that, while the combination of a fast event-related task design with BOLD-fMRI is not optimal, such a combination has—despite the drawbacks and a reduced signal-to-noise-ratio—yielded important insights into the neural basis of inhibition in prior studies (36, 63).

Pre-processing and Analysis of Functional MRI Images

Pre-processing

Task-fMRI images were preprocessed using the routines implemented in SPM12. Initially, the origins of all functional and anatomical images were reoriented to the anterior commissure. The field map images were used to construct the voxel displacement map for unwarping, which was applied after realignment that involves participant's motion correction. Subsequently, slice time correction was run as well as coregistration of the functional images to the anatomical image. A brain tissue segmentation was performed to obtain forward deformation fields for the image normalization procedure, which transformed the images to the MNI standard space. Finally, all functional images were smoothed using a 3D-Gaussian Kernel with 6 mm^3 FWHM.

First-Level Analysis

In order to extract functional activation images for each GNG stimulus condition, contrast images at the subject level were generated (e.g., 1st-level analysis). For this purpose, the preprocessed images were entered to a general linear model (GLM). In detail, a design matrix was constructed with the predefined GNG task events consisting of stimulus type (ALC, NEU), response type (NoGo, Go), and participant's response accuracy (correct, error). We used the canonical hemodynamic response function (HRF) as a basis function that was convoluted with the onsets of the resulting eight event types ($NoGo_{ALC\_correct}$, $NoGo_{NEU\_correct}$, $Go_{ALC\_correct}$, $Go_{NEU\_correct}$, $NoGo_{ALC\_error}$, $NoGo_{NEU\_error}$, Go_{ALC_error}, and Go_{NEU_error}). The six individual motion parameters derived from realignment were entered as regressors of no interest to the design matrix. Finally, the GLM was estimated. For calculation of contrast images, only parameter estimates of regressors corresponding to event types with correct participant responses were included, since this study focused exclusively on successful inhibition. Thus, the following four contrasts were computed: $(NoGo_{ALC} + NoGo_{NEU}) > (Go_{ALC} + Go_{NEU})$, $NoGo_{ALC} > Go_{ALC}$, $NoGo_{NEU} > Go_{NEU}$, $(NoGo_{ALC} > Go_{ALC}) > (NoGo_{NEU} > Go_{NEU})$.

Second-Level Analyses

These first-level contrast images were used to calculate random effects at the group or second level. First, we investigated whether neuronal activation during alcohol-specific inhibition increases with craving (assessed with OCDSimp). To this end, a whole-brain linear regression was performed with $NoGo_{ALC} > Go_{ALC}$ with OCDSimp as the covariate of interest. A second linear regression using $NoGo_{NEU} > Go_{NEU}$ and OCDSimp as the covariate was performed to tests whether results were specific for alcohol-related inhibition. In order to have this analysis encompass a broad spectrum of craving levels, healthy controls were included in this analysis in addition to patients with AUD (see right panel of **Figure 1**), leading to an analytic sample of $N = 70$. For this analysis fMRI-data from the pre-training session was used.

Second, a planned contrast $(NoGo_{ALC} > Go_{ALC}) > (NoGo_{NEU} > Go_{NEU})$, which isolates alcohol-specific inhibitory activation, was used for exploring whether the neurophysiological signature of alcohol-specific inhibition is predictive for drinking outcomes. More detailed, the individual planned contrast whole brain images (from the pre-training fMRI session) of $N = 35$ patients with AUD were used in a whole brain linear regression with the drinking outcome (indicated by PDA Δ) as the covariate of interest. This analysis thus used the fMRI data from the pre-training session to predict drinking outcome at 3-months follow-up. For this analysis, only gray matter voxels were used by applying a binary mask derived from the mean over all individuals' MP2RAGE gray matter segmented image. Brain regions yielded by this analysis as reflecting a neural

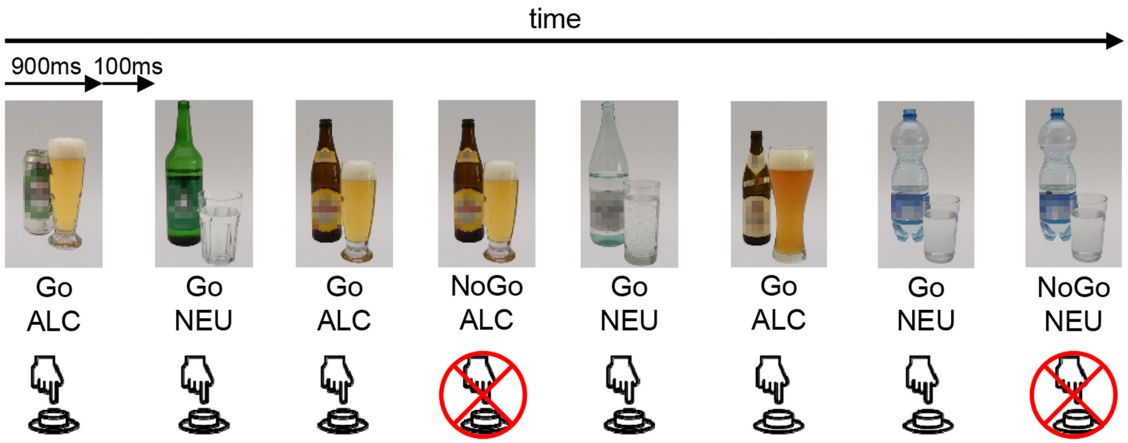

FIGURE 2 | Schematic illustration of the GNG event-related fMRI task. The stimuli are either an alcoholic bottle with a glass (ALC) or a neutral (i.e., water) bottle with a glass (NEU). This is an example of the beer set, whereas depending on the participant's preference, also wine or spirits sets were available. Participants were instructed to press a button whenever a stimulus appeared (Go), unless the exact same stimulus was shown twice successively (NoGo).

correlate of alcohol-specific inhibition which is predictive of relapse, will be used as regions of interest (ROIs) in the third analysis (see below).

Third, to investigate whether the thus functionally defined, relapse-predicting, alcohol-specific inhibitory activation can be altered through training, the MNI-coordinates of potential effects yielded by the second whole-brain analysis served as regions of interest (ROIs). From these ROIs, beta-values were extracted for each subject, for which a complete dataset was obtained. The analytic sample of this third analysis consisted of $N = 31$ patients with AUD, for which pre-training fMRI data, post-training fMRI data, and drinking outcome data at 3-months follow-up was available. The beta-value analysis was applied to investigate whether the magnitude of alcohol-specific inhibitory activation predictive for drinking outcome was modulated by the training. Therefore, a 2 × 2 × 2 × 2 repeated-measures ANOVA was conducted using the beta-values of the potential ROIs as dependent variable and featuring the between-subject factor training (Alc-IT/Control) and the three within-subject factors response type (NoGo/Go) × stimulus type (ALC/NEU) × pre-post (pre-training/post-training). A significant 4-way interaction was needed to confirm a training-effect on alcohol-specific inhibition in the potential ROI that is predictive for drinking outcome.

For completeness, a basic analysis used the (NoGoALC + NoGoNEU) > (GoALC + GoNEU) contrast (pre-training images only) in one-sample *t*-tests run separately for the AUD and HC groups with the aim of contributing to the research on general inhibition in AUD. As general inhibition was not the main focus of this study, these results can be found in the **Supplementary Figures 1, 2**.

Statistical Analyses

Statistical Package for Social Sciences (SPSS, version 28, IBM Corp., Armonk, NY, USA) was used to assess group differences of demographics and clinical scores. All variables except the BDI II score were non-normally distributed. Therefore, to test differences between the two AUD subgroups, non-parametric Kolmogorov-Smirnov tests were run. For differences over all three groups, non-parametric Kruskal-Wallis tests were computed. Behavioral GNG data [reaction times (RTs), errors of commission (EOC), errors of omission (EOO)] were non-normally distributed and therefore analyzed with ANOVA-type non-parametric statistics using the nparLD package in R (64). This analysis was run twice, first including factors AUD and HC as group variable, and second with factors Alc-IT and control training as group variable. For statistical inference involving voxel-wise fMRI-data (linear regression with $\text{NoGo}_{\text{ALC}} > \text{Go}_{\text{ALC}}$ and OCDSimp, linear regression with $\text{NoGo}_{\text{NEU}} > \text{Go}_{\text{NEU}}$ and OCDSimp, linear regression with planned contrast and PDA Δ, and one-sample *t*-tests with NoGo > Go), SPM12 routines were applied with a family-wise error (FWE) correction at critical *p*-value threshold of 0.05, with a cluster size of 0. The repeated-measures ANOVA involving beta-values of the ROI was computed with SPSS. Anatomical brain and activation illustrations were created using the MRIcroGL software (https://www.nitrc.org/projects/mricrogl/). Finally, statistics necessary to produce illustrations (**Figures 3**, **4**) were calculated with R (v4.1.0).

RESULTS

Descriptive and GNG Behavioral Statistics

While the three study groups did not differ in age, the HC group showed a higher education level than the AUD group. As expected, the HC group scored lower in BSCL GSI, OCDSimp, and OCDSsum scores than the AUD group. All group means as well as group statistical *p*-values can be found in **Table 1**. Important for comparisons between the two AUD training groups, no differences were found in any demographic or clinical variable. Underlining the validity of the OCDSimp scale, which was used to operationalized craving, correlations between

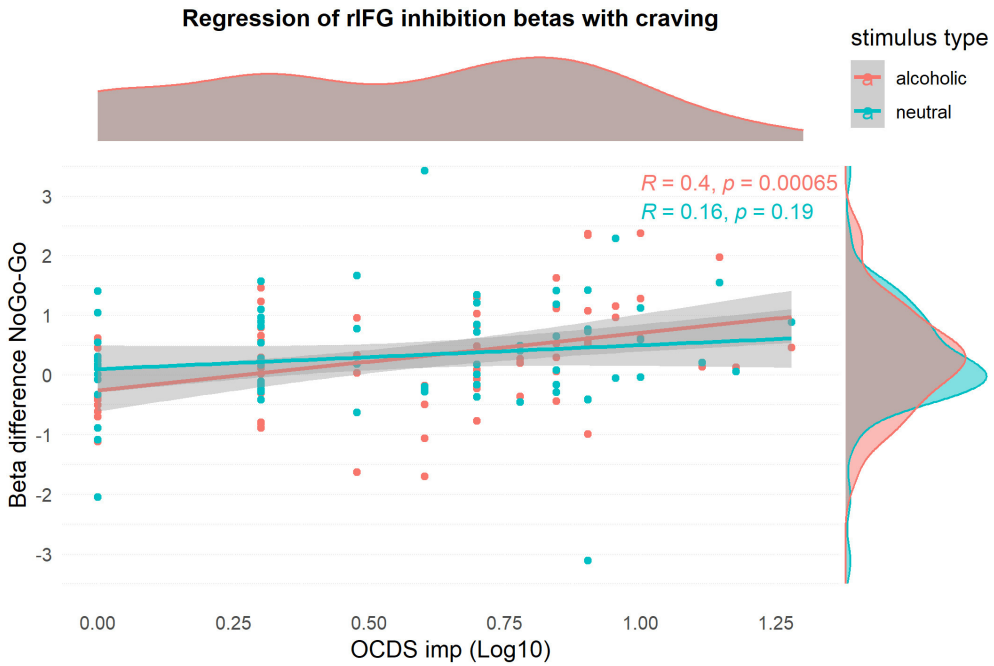

FIGURE 3 | Visualization of the relationship of rIFG beta-values and log10-transformed OCDSimp scores, stratified for stimulus type. The graph confirms that craving has a positive relationship with inhibition activation during alcohol-related inhibition only.

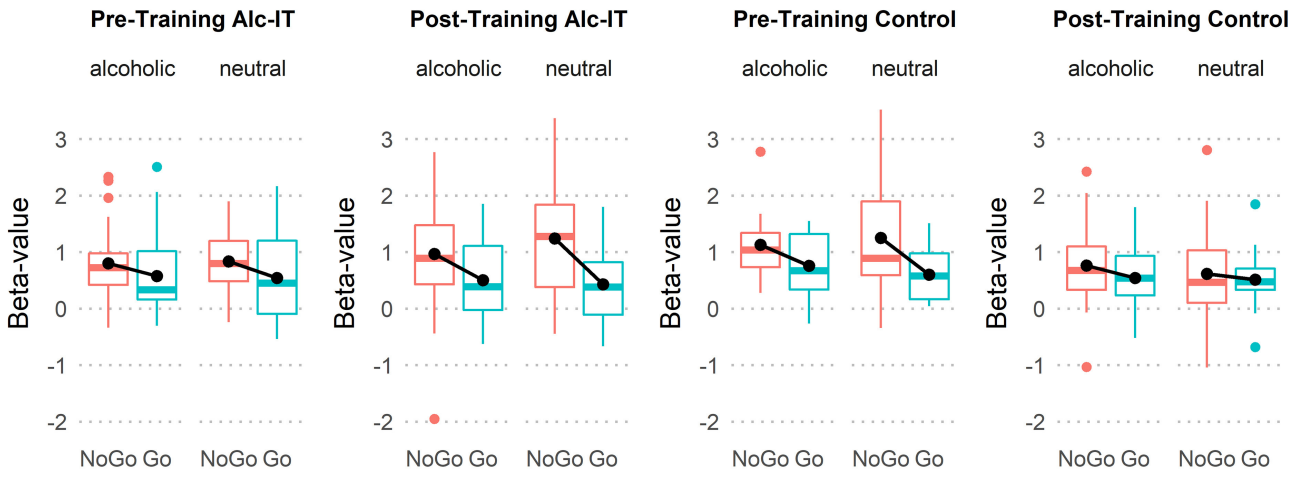

FIGURE 4 | Boxplots indicating beta-value differences of response type (NoGo in red, Go in green), stimulus type, pre- and post-training, and training type. Black lines connecting black dots highlight mean-differences in inhibition activation.

OCDSimp and a visual analog scale to assess craving are shown in **Supplementary Figure 3**.

Analyzing the GNG behavioral data from the pre-training measurement, both AUD and HC made more EOCs with NEU trials than ALC trials as confirmed by a significant main effect of stimulus type [ANOVA-type-statistics $(ATS)_{(1)} = 7.25$, $p = 0.007$]. EOCs, the main indicator of inhibitory performance, did however not differ between patients with AUD and HCs. The RTs of EOC were significantly shorter in NEU than ALC [$ATS_{(1)} = 5.15$, $p = 0.023$], and shorter in HC compared to AUD [$ATS_{(1)} = 4.92$, $p = 0.027$], although the two-way interaction was not significant [$ATS_{(1)} = 0.36$, $p = 0.548$]. Concerning the number of EOOs the AUD group performed worse than the HC group [$ATS_{(1)} = 5.48$, $p = 0.019$]. Again, the interaction was not significant [$ATS_{(1)} = 0.16$, $p = 0.686$]. RTs in correct Go trials were shorter in HC compared to AUD [$ATS_{(1)} = 7.40$, $p = 0.007$], with no significant stimulus type × group interaction [$ATS_{(1)} = 0.32$, $p = 0.573$].

The next analysis compared the patients' GNG behavioral data between the two training groups (Alc-IT, Control) and both timepoints (pre taining/post training) and stimulus types (ALC, NEU). This analysis indicated that numbers of EOC were higher in NEU than ALC [$ATS_{(1)} = 12.38$, $p < 0.001$]. The two-way [pre/post-training × training type: $ATS_{(1)} = 4.94$, $p = 0.026$] and three-way interaction (stimulus type × pre/post-training × training type) were also significant [$ATS_{(1)} = 6.11$, $p = 0.013$]. Follow-up analyses of these interactions showed that only in the NEU condition, but not in the ALC condition, the two-way interaction (pre/post-training × training type) was significant [NEU stimulus type: $ATS_{(1)} = 11.18$, $p < 0.001$; ALC stimulus type: $ATS_{(1)} = 0.35$, $p = 0.555$]. Subsequent simple effects analyses indicated that EOCs in the NEU condition only decreased in the control training [pre/post-training effect: $ATS_{(1)} = 15.39$, $p < 0.001$], and not the Alc-IT training type [$ATS_{(1)} = 1.85$, $p = 0.174$]. When analyzing the two-way interaction of stimulus type and pre/post-training separately for each training group, this interaction was not significant in both groups [Alc-IT: $ATS_{(1)} = 2.71$, $p = 0.100$; Control: $ATS_{(1)} = 2.58$, $p = 0.108$].

Such effects were not found in the RTs of EOC [all effects $ATS_{(1)} < 1.55$, $p > 0.21$]. In the number of EOO, main effects of pre/post-training [$ATS_{(1)} = 4.62$, $p = 0.032$], and stimulus type [$ATS_{(1)} = 12.61$, $p < 0.001$] were found. In particular, the number of EOO was higher pre- compared to post-training, and higher for ALC compared to NEU. Finally, correct response RTs in the Go condition were shorter post than pre training RTs [$ATS_{(1)} = 19.53$, $p < 0.001$]. Means and standard deviations of the analyzed GNG behavioral variables can be found in **Supplementary Tables 1, 2.**

Does Neuronal Activation Related to Alcohol-Specific Inhibition Increase With Craving?

Linear Regression of Alcohol-Specific Inhibitory FMRI Data With OCDSimp

This analysis was performed to identify brain regions, where alcohol-specific inhibitory activation increased with craving. Using the $NoGo_{ALC} > Go_{ALC}$ contrast, a small ROI was found in the right inferior frontal gyrus, which showed a positive relationship between brain activation and OCDSimp scores (**Table 2**, **Figure 5**). This indicates that alcohol-related inhibitory brain activation in rIFG was higher in those subjects reporting high craving as compared to subjects with low craving. Contrary to that, the $NoGo_{NEU} > Go_{NEU}$ contrast yielded no significant clusters (**Supplementary Figure 4A**). Using the beta-values of the rIFG ROI, **Figure 3** illustrates that the correlation of craving and inhibitory brain activation was specific for alcohol-related stimuli. *Post-hoc* analyses inspecting the correlation between inhibitory activation in the IFG ROI and craving separately for the patient group replicated this result and indicated that for patients, craving levels correlated significantly with alcohol-related rIFG activation (**Supplementary Figure 4B**).

TABLE 2 | SPM output listing significant cluster with statistics and MNI-coordinates of the regression analyses investigating gray matter whole brain relationships of inhibition activation and craving as well as drinking outcome.

	Peak-level					
Atlas label[a]	$p_{FWE\text{-}corr}$	***T***	k_E	**mm**	**mm**	**mm**
Alcohol inhibition/craving						
rIFG, pars opercularis	0.032	4.87	4	48	18	12
Planned contrast/drinking outcome						
rIFG, pars opercularis	0.005	6.73	9	48	12	8
rIFG, pars opercularis	0.021	6.10	2	62	16	16

[a] *Harvard-Oxford Cortical Structural Atlas.*

kE, cluster extend; pFWE-corr, p-value yielded by analysis using family-wise error correction; rIFG, right inferionr frontal gyrus.

Is the Neurophysiological Signature of Alcohol-Specific Inhibition Related to Drinking Outcomes?

Linear Regression of Planned Contrast FMRI Data With PDA Δ

This analysis was conducted to identify possible regions of interest, where the activation during alcohol-specific inhibition (as isolated in the planned contrast) predicts drinking outcome (as indicated by PDA Δ) in the patients with AUD. **Table 2** lists the statistics and MNI coordinates of two significant clusters that showed a positive relationship between alcohol-specific inhibitory activation and PDA Δ. No significant clusters were found with a negative relationship. In accordance with Eklund et al. (65) we report peak-level statistics rather than cluster-level statistics. Hence, higher alcohol-specific inhibition activation in the regions found in the right inferior frontal gyrus is predictive for a better drinking outcome. While both regions are comparably small in cluster extent, we limited our *post-hoc* analysis only on the larger of the two regions. **Figure 5** illustrates the anatomical localization of the larger region superimposed on the mean gray matter image of the study cohort.

Can the Neurophysiological Signature of Alcohol-Specific Inhibition Be Altered Through Alcohol-Specific Inhibition Training?

ANOVA Using RIFG Beta Values and Assessing Potential Training Effects

This analysis aimed at investigating whether Alc-IT had a beneficial effect on the alcohol-related inhibitory activation in the rIFG ROI identified in the previous analysis. **Figure 4** displays boxplots providing an overview of the rIFG beta values for each response type, stimulus type, pre-training and post-training session, and training type. The 2 × 2 × 2 × 2 repeated-measures ANOVA yielded a main effect of inhibition [$F_{(1,29)} = 14.7$, $p < 0.001$, $\eta^2 = 0.336$], showing higher activation in NoGo compared to Go trials. Moreover, a significant three-way interaction of response type × pre- post-training × training type [$F_{(1,29)} = 4.4$, $p = 0.045$, $\eta^2 = 0.132$] indicated that Alc-IT has

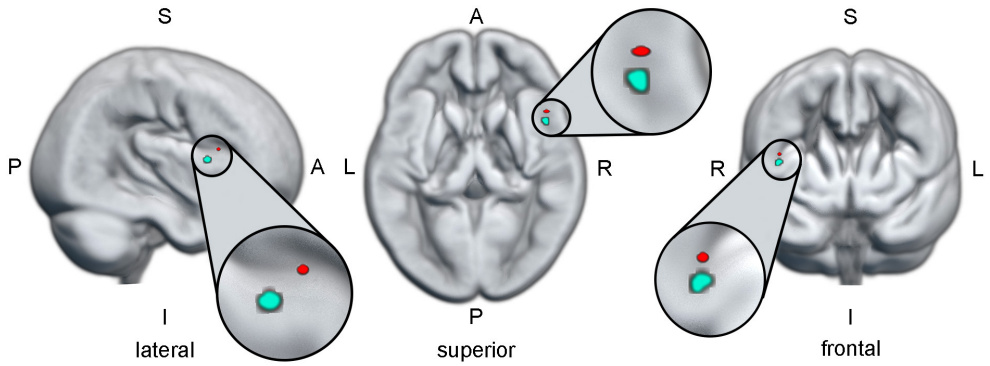

FIGURE 5 | The red dot indicates the region in the right inferior frontal gyrus, where a higher activation during alcohol-related inhibition is predictive for higher craving. The cyan dot indicates the region in the right inferior frontal gyrus, where a higher activation during alcohol-specific inhibition is predictive for a better drinking outcome. The anatomical brain render used for this illustration is based on the mean normalized gray matter image of all participants included in this study. All three views were cut from the surface to the localization of the cyan ROI. Since the red ROI is on the same pane as the cyan ROI only in the lateral view, the red ROI should be viewed as "hovering in the air" in the superior and frontal views. A, anterior; I, inferior; L, left; P, posterior; R, right; ROI, region of interest; S, superior.

an effect on inhibition activation in general, but not specifically on alcohol-related inhibition. This interaction can be seen in **Figure 4** when inspecting the slope of the black lines reflecting the magnitude of inhibitory activation. Specifically, the slope steepness seems to increase from pre-training to post-training in Alc-IT, whereas it appears to decrease in control training. However, the target four-way interaction was not significant [$F_{(1,29)} = 1.6, p = 0.213, \eta^2 = 0.053$], opposing to our hypothesis of a beneficial effect of Alc-IT on alcohol-specific inhibition (at least in the ROI analyzed).

DISCUSSION

Analyzing fMRI data collected during an alcohol-related GNG task, this study set out to investigate whether neurophysiological correlates of alcohol-specific inhibition (I) vary with craving (see Section Does Neuronal Activation Related to Alcohol-Specific Inhibition Increase With Craving?); (II) are related to drinking outcomes in AUD (see Section Is the Neurophysiological Signature of Alcohol-Specific Inhibition Related to Drinking Outcomes?) and (III) can be altered through alcohol-specific inhibition training (see Section Can This Relapse-Predicting Neurophysiological Signature of Alcohol-Specific Inhibition Be Altered Through Alcohol-Specific Inhibition Training?).

Does Neuronal Activation Related to Alcohol-Specific Inhibition Increase With Craving?

In a small cluster of the right inferior frontal gyrus (rIFG), the neurophysiological correlates of alcohol-related (but not neutral) inhibition increased with craving, indicating that brain activation during alcohol-related inhibition was higher in those subjects, which experienced higher levels of craving. This finding extends earlier reports of craving being linked to enhanced neurophysiological activation in cingulate areas during alcohol-specific inhibition (31, 42) to the rIFG. While it supports the general idea of higher craving being linked to enhanced neurophysiological activation during successful alcohol-specific inhibition, one must acknowledge that the specific locations do not align across studies. This might be due to differences in stimulus material (31, 42) or due to EEG (42) and fMRI measuring non-overlapping aspects of the neuronal activation.

The rIFG is part of the cognitive control network (66, 67) and particularly the pars opercularis (68) has been shown to be selectively activated by tasks requiring response inhibition (22, 23). Recent reviews of neurofunctional networks involved in addictive disorders feature the IFG as a central node of a dysregulated inhibitory control network in substance use disorder (SUD) (4, 5). In patients with SUD, higher rIFG activation was furthermore linked to decreased attentional impulsiveness (69) and to a better ability to ignore drug-related stimuli during a working memory task (70), supporting its role in suppressing cue-induced responses. Higher rIFG activation during successful alcohol-related inhibition, which we observed in those patients reporting higher craving, might thus be indicative of additional neuronal resources being necessary in order to control responses in the face of highly salient and reward-predicting stimuli.

Is the Neurophysiological Signature of Alcohol-Specific Inhibition Related to Drinking Outcomes?

Again in the rIFG, neurophysiological activation during alcohol-specific inhibition was related to a better outcome, as indicated by a higher percentage of days abstinent at 3-month follow-up. Those patients displaying a higher activation difference in the rIFG for alcohol-related (as compared to neutral) inhibition reported more days abstinent at 3-months follow-up. The outcome was thus better in those patients, who managed to recruit enhanced neuronal resources during inhibition when the inhibitory system had to oppose cue-induced appetitive processes.

As summarized above, the rIFG is closely linked to effective inhibition and has been linked to response suppression in the face of craving and cue-induced reactions (4, 70). Our results thus suggest that enhanced inhibitory rIFG activation in the face of alcohol-related stimuli might enhance the chance to inhibit potential drinking urges or automatized drinking habits and thus fosters abstinence in patients with AUD. Such an interpretation is in line with an earlier study indicating that the neurophysiologic correlate of alcohol-specific inhibition, as measured with event-related potentials, predicts relapse in AUD (43). More closely related to the rIFG, an earlier fMRI study in patients with AUD also linked stress-induced activation in the right ventrolateral PFC, which includes the rIFG, to alcohol use in a 90-day follow-up period [(71), note however that in the same study, a linkage between alcohol-induced cue reactivity and relapse could not be deteccted].

Taken together, the present results indicate that higher rIFG activation is necessary to inhibit responses to alcohol-related cues when craving is high. In line with this, as most patients with AUD probably experience situations with high craving when returning to everyday life after residential treatment, enhanced IFG activation during alcohol-specific inhibition predicts a better outcome at 3-months follow-up.

Can This Relapse-Predicting Neurophysiological Signature of Alcohol-Specific Inhibition Be Altered Through Alcohol-Specific Inhibition Training?

A training effect on the neurophysiological correlate of alcohol-specific inhibition in the rIFG could not be observed; rIFG activation was not modulated by patients engaging in alcohol-related inhibition training (Alc-IT) vs. an unspecific inhibition training (control). Thus, we cannot conclude that this neurophysiological correlate, which—according to the analyses reported above—varies with craving and predicts drinking outcome, is affected by the alcohol-specific inhibition training. In that respect, our results differ from reports on another cognitive training intervention, approach bias training, where training effects on brain activity could be observed, albeit in ROI analyses focusing on other brain regions and during different tasks (72, 73). One possible explanation is the limited statistical power in this study, which was smallest for this third research question due to the complex design and the restriction to those patients providing follow-up data. Furthermore, it might be that neurophysiological effects of Alc-IT are better detectable with neurophysiological methods allowing for a higher temporal resolution (74). Also, we focused our analyses of training effects on a ROI in the rIFG, which was functionally defined as the region in which we found alcohol-specific inhibitory effects related to relapse. This analytic approach was conceptually motivated by prior research supporting the hypothesis that Alc-IT enhances alcohol-specific inhibition and might reduce relapse risk (3). However, it is also conceivable that Alc-IT produces training effects centered in other regions of the brain. Such effects would have been overlooked by the present ROI analyses and might be too small to be detected in a whole brain analysis (which we conducted *post-hoc* with no significant results). To be complete, one should mention that the neurophysiological correlate of general (but not alcohol-specific) inhibition was differentially affected in the group receiving Alc-IT when compared to control training. As there was however no theoretical justification for a ROI-analysis focusing on this three-way interaction in the rIFG, this finding has to be seen as highly exploratory.

As a general limitation, one might argue that the effects reported above are very small. The resulting clusters were smaller than 10 voxels in extent. Besides the FWE-correction, no additional cluster size threshold was applied. None of the three clusters reported in **Table 2** would be significant with the even more conservative topological FDR-correction, and only the largest cluster would remain significant using the TFCE-method ($p_{FWE-corr} = 0.030$; $T = 5.95$; $k_E = 3$; x = 48 mm; y = 12 mm; z = 8 mm). Besides the fact that the application of the FWE-correction used here is a common way to minimize type-I errors, one should however take into account two important aspects: (I) Alcohol-specific inhibitory activation, as we attempted to isolate it in this study, is reflected in a highly specific effect. Our analyses thus had to concentrate on those inhibitory sub-processes that vary with the context in which inhibition had to be carried out. On the one hand, such a highly specific effect might be represented on smaller sub-regions. On the other hand, such an effect might also be harder detectable in a noisy signal such as BOLD. One might therefore consider the application of higher field strengths (e.g., 7 Tesla), where a higher signal should be expected and where the higher spatial resolution might also allow a better investigation of subregions of IFG. (II) The spatial extend of the rIFG clusters amounted to 32 and 72 mm^3, respectively. With a neuronal density of several thousand per mm^3, we should not preclude that activation of such a specific cognitive process is possible within these small regions, unless there exists indication that it is impossible. In addition, it appears unlikely that two different whole-brain analyses yielded exclusively two highly proximal clusters in a region central to inhibition (66, 68) purely by chance. Therefore, in order to avoid not only type I, but also type II errors (75), the present results should be considered as neurophysiologically meaningful, which should of course be corroborated by replication in future studies.

Another limitation concerns the task design. Compared to earlier studies (31, 42), the present task employed a limited number of different alcohol-related pictures. This led to each picture being displayed more often than in earlier studies and might have facilitated habituation, which might have dampened effects related to alcohol-specific inhibition.

While the behavioral performance on the Go-NoGo task was not the focus of this study, two aspects are still worth noting. A first aspect concerns the fact that in the present study, patients with AUD did not display an inhibitory performance deficit (as indicated by errors of commission (EOCs) during NoGo trials). This is inconsistent with the overall pattern yielded by meta-analyses summarizing behavioral studies on inhibitory performance (8, 9) and with some studies on neurophysiological

correlates of inhibition in substance use disorder (36, 37). However, it is in line with other neurophysiological studies on inhibition in substance use disorder (25, 26, 29, 34, 76). In the literature, these inconsistencies are discussed with respect to the stimulus material and task context (alcohol-related or neutral)(4), to methodological details (17) as well as to differences in the specific stud samples ability recruit the necessary additional neuronal resources to achieve a comparable performance (5, 31).

A second aspect concerns the fact that no effect of the Alc-IT training intervention on alcohol-related EOCs could be detected. As studies on behavioral effects of cognitive training interventions are often larger, this might either be due to a limited power or to the fact that Alc-IT really did not affect alcohol-related errors of commission.

In summary, the present study corroborated the central role of the rIFG in the inhibitory control network in AUD by indicating that rIFG activation during alcohol-related inhibition is related to craving and drinking outcome. Therefore, as has been proposed before in the context of cocaine addiction (69), future studies might investigate under which circumstances rIFG activation might potentially serve as a biomarker for increased relapse risk.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because no consent for this was collected from patients. Processed data and corresponding processing subroutines can be requested from the corresponding author. Requests to access the datasets should be directed to maria.stein@upd.unibe.ch.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee (KEK-number: 2016-00988) and registered at the Swiss National Clinical Trials Portal (SNCTP000002043) and ClinicalTrials.gov (NCT02968537). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG collected the data, conceptualized and performed data and statistical analyses, and wrote the manuscript. LS and FM designed the study and supervised data collection and data curation. RT and HB collected the data. AF conceptualized and performed data and statistical analyses. SS collected the data and conceptualized data analyses. YM supervised data collection and data curation. MS designed the study, supervised data collection and data curation, conceptualized data and statistical analyses, and wrote the manuscript. All authors contributed to discussion and interpretation of the results, revised, and approved the final version of the submitted manuscript.

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SUPPLEMENTARY MATERIAL

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Effects of moderate-intensity exercise on social health and physical and mental health of methamphetamine-dependent individuals: A randomized controlled trial

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Objective: Methamphetamine (MA)-dependent individuals' health problems are widespread and need to be solved urgently. Exercise is considered a potential treatment for MA dependents. The study aimed to determine the effects of a 12-week aerobic exercise on the social, physical, and mental health of MA-dependent individuals.

Materials and methods: Sixty MA-dependent individuals were randomly assigned into two groups. Subjects in the exercise group (n = 30) received an exercise intervention five days a week for 60 min each for 12 weeks. Subjects in the control group (n = 30) received regular corrective rehabilitation without exercise in the same setting. Outcome measures, including questionnaires [quality of life scale for drug addiction (QOL-DA), self-rating anxiety scale (SAS), self-rating depression scale (SDS), and Pittsburgh sleep quality index (PSQI)] and physical fitness, were arranged the day before the start of the intervention and the day after the end of the intervention. Two-factor repeated measures ANOVA was used to compare the treatment differences between the two groups.

Results: After 12 weeks of the intervention period, social health was significantly improved in the exercise group ($P < 0.01$), and there was a statistically significant difference in mental health scores between exercise group and control group, with a greater impact in exercise group.(Psychology: $P < 0.01$; SAS: $P < 0.01$; SDS: $P < 0.01$; PSQI: $P < 0.01$), physical health improved in the exercise group, physiology ($P < 0.01$), symptom ($P < 0.01$), heart rate ($P < 0.01$), systolic blood pressure ($P < 0.01$), systolic blood pressure ($P < 0.01$), vital capacity ($P < 0.05$), grip ($P < 0.01$), vertical jump ($P < 0.001$), sit and reach ($P < 0.01$), 50-meter run ($P < 0.01$), and reaction time ($P < 0.01$).

Conclusion: Aerobic exercise intervention is an effective treatment for MA-dependent individuals, and the 12-week intervention improved the social, physical, and mental health of MA-dependent individuals. We recommend that future studies focus more on drug-dependent individuals' overall health status rather than just relapse.

Clinical trial registration: [https://www.chictr.org.cn/hvshowproject.aspx?id=131048], identifier [ChiCTR2200055348].

KEYWORDS

methamphetamine, exercise, social health, addiction, treatment

Introduction

Health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (1). Among them, social health is considered a dynamic balance between opportunities and limitations; the constant changes in life, society, and the environment bring endless restrictions and challenge people's ability to adapt to this state (1). Methamphetamine (MA) is a powerful, illicit psychostimulant (2, 3) that causes some degree of impairment to social, physical, and mental health when ingested. The clinical response to acute MA use is characterized by euphoria, reduced fatigue, and social activation (4, 5), leading to a false "ideal state of health." However, the legacy of mental impairment from substance use can eventually lead to impaired social functioning and even isolation in MA abusers (6). At the same time, poor social competence will reinforce addictive behaviors, including MA (7, 8), creating a vicious cycle, whereas positive social interactions can prevent drug addiction to some extent (9). Furthermore, the damage to physical health from MA abuse is reflected in the increasing deterioration of physical function, cardiorespiratory and cardiovascular function, and all of its related physical indicators. Long-term use of MA has deleterious effects on motor function and muscles (10), causes excessive pulmonary stress (11), increases vascular damage, leads to persistent vascular dysfunction, and accelerates atherosclerosis (12–14). Finally, among psychological conditions, depression and anxiety are the most common disorders (15), and depression has been recognized as a hallmark of MA withdrawal symptoms (16), which may be because of abnormalities in monoamine neurotransmitter pathways, such as dopamine, serotonin, and norepinephrine, as a result of MA abuse (17, 18). Sleep difficulties during MA withdrawal are also a relatively rare symptom compared with other drugs of abuse (4). The poor impact of MA abuse on social, physical, and mental health leads to high relapse rates (19, 20) and is also accompanied by higher suicide attempts (21, 22). New evidence suggests that methamphetamine abuse may become the next substance abuse crisis worldwide (23, 24).

Physical exercise is considered a potential treatment for MA addiction (25–27). And numerous mechanisms have been proposed to explain why exercise can improve the health of MA-dependent individuals, including the improvement of the nervous system, the improvement of the inhibitory control ability, the recovery of the monoaminergic system, the recovery of the blood-brain barrier, and the remodeling of cortical function (28–32). Indeed, clinical trials indicate long-term aerobic exercise is effective in reducing depressive and anxious emotional states and improving physical health and quality of life in MA-dependent individuals (33). Aerobic exercise improves physical health indicators, such as lung capacity, grip strength, and standing on one foot with eyes closed, in MA-dependent individuals (34, 35). Meanwhile, a recent meta-analysis suggested that exercise showed better therapeutic effects on the physical health of ATS-dependent individuals (35). In addition, exercise training three times a week can enhance heart rate variability in MA-dependent individuals by increasing the balance between vagal regulation and autonomic control (36), intending to protect cardiovascular function in MA-dependent individuals. A recent systematic review demonstrated that exercise can be effective in regulating addiction in drug-dependent individuals while serving as a stress management tool to improve their mental health (37). Level II evidence suggests that exercise is effective in reducing anxiety and depression in MA-dependent individuals (38). Also, clinical trials have found significant improvements in depression and anxiety symptoms in newly admitted MA-dependent individuals who received an eight-week exercise intervention, and the effects continued to be significant over time (39). For social health, research has found that physical activity can facilitate the establishment of positive social contact among substance use disorders (40). In addition, group-based exercise has been shown to have significant benefits on the social functioning of drug-dependent individuals (41). There is a paucity of research on the social health of MA dependents with exercise therapy and a lack of evaluation of the effects of exercise therapy on them from an overall health perspective.

Therefore, the present study attempted to assess the effects of moderate-intensity aerobic exercise on the social,

physical, and mental health of MA-dependent individuals from a health perspective. Also, expand the research direction in this field. Based on the existing studies and literature, we hypothesized that moderate-intensity aerobic exercise could improve the social, physical, and mental health of MA-dependent individuals.

Materials and methods

Study design

This study used a single-blind (assessor-blind), randomized, clinical, parallel-group intervention. The recruitment of participants and the conduct of the trial were conducted at the Ziyang Drug Rehabilitation Institute in Sichuan Province. Open recruitment was adopted to recruit willing subjects by conducting a centralized presentation to drug addicts in the institute. The study was approved by the Ethics Committee of the Chengdu Sports University [Grant No. (2021) 14] and all experimental procedures followed the Declaration of Helsinki, a guideline for human medical research (42). All participants provided written informed consent. The current study has been registered on the platform of the China Trial Registration Center (Registration number: ChiCTR2200055348).

Sample size

The sample size required for the current trial was calculated by PASS 15.0 statistical software. Based on a previous report (43), using an independent samples *t*-test, set at $\alpha = 0.05$ (two-sided) and $\beta = 0.1$, we estimated that a sample size of 22 cases per group was required after allocation, and considering a 15% loss to follow-up rate of study participants, a minimum of 26 participants per group should be secured. Ultimately 30 participants were included in each group in this study.

Participants

A total of 63 MA-dependent individuals were recruited for this study at Ziyang Drug Rehabilitation Center in Sichuan Province, of which three subjects did not meet the inclusion criteria. A total of 60 validated MA-dependent individuals were recruited after screening by strict inclusion and exclusion criteria. General information, including age, height, weight, occupation, marital status, years of drug use, and average dose of drug use, were collected from the study subjects who met the inclusion criteria. The subjects were randomly assigned to the exercise intervention group ($n = 30$) and the conventional treatment group ($n = 30$) by another researcher not involved in this study using the random number table method. In brief, 60 participants were assigned numbers (1, 2, 3.60) recorded in an Excel sheet, and then 60 random numbers were generated, after which they were sorted in ascending order, with the top 30 being included in the exercise group and the bottom 30 in the control group. The flowchart of the experimental procedure is shown in **Figure 1**.

Inclusion and exclusion criteria

1. Inclusion criteria: (1) between 18–55 years old and eligible for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-?) methamphetamine substance dependence, (2) with elementary school education or above, (3) assessed to be free of exercise risk, (4) can guarantee more than six months of recovery time, (5) voluntarily participated and signed an informed consent form.

2. Exclusion criteria: (1) with infectious diseases, such as hepatitis and the human immunodeficiency virus (HIV) and serious untreated trauma; (2) with recent neurological injuries, such as cranial brain injury and spinal cord injury, neurodegenerative diseases, or serious psychiatric diseases; (3) suffering from serious organic diseases; (4) with addictive behaviors other than methamphetamine addiction; (5) having ingested drugs, such as methadone, for addiction treatment within the last four months.

Exercise intervention

The exercise intervention program was moderate-intensity aerobic exercise according to Physical Activity Guidelines for Chinese (44). Based on dose-response studies, moderate-intensity exercise appears to be the optimal intensity for treating substance use disorders (45–47). The exercise group received moderate-intensity aerobic exercise for 1 h 5 times per week for 12 weeks. The exercise program includes 10 min of warm-up training (jogging, warm-up activities or dynamic stretching), 30 min of aerobic training (cycling, jogging or calisthenics), and 20 min of stretching (static stretching for the training area) each day. The exercise program was performed by two master's degree students in kinesiology, and the participants' real-time heart rate was monitored by a polar heart rate sensor (BHT Gofit 3.0), which was used to control the intensity of exercise during the one-week adaptation period (65–70% HRmax; HRmax = 206.9–0.67*age), and the heart rate was controlled at (70–75% HRmax) (48). To ensure that all subjects received the same exercise intervention, one interventionist led the training while the other supervised the subject's movements to meet the standards and monitored the subject's heart rate in real time via a mobile device. The control group received regular corrective rehabilitation treatment in a rehabilitation institution, including educational correction, group counseling, etc. (the matrix model was not adopted), and did not perform any exercise and was scheduled to perform at the same time

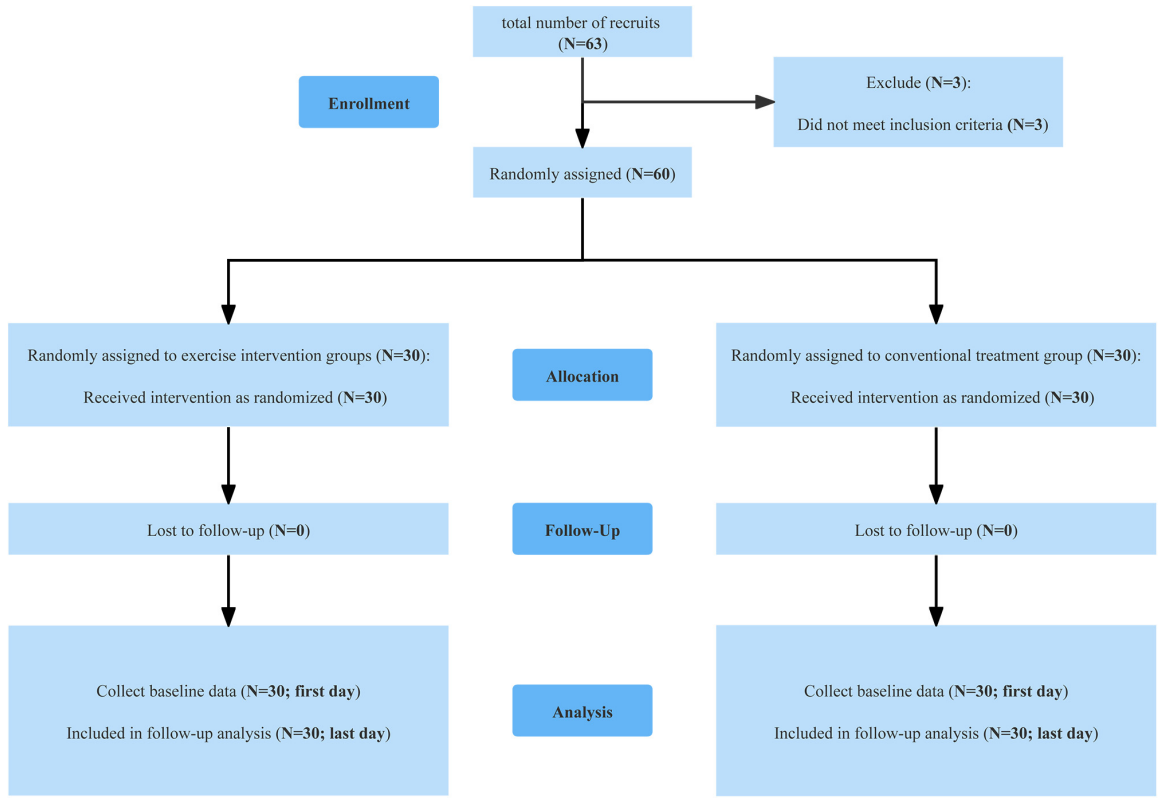

FIGURE 1
Flow-chart of the experimental procedure.

as the exercise group. The rest of the time, the two groups lived the same lives.

Outcome

The primary outcome was the social health of the subjects, which is measured with the quality of life scale for drug addiction (QOL-DA) (49). Quality of life covers the whole spectrum of health (physical, psychological, social, etc.) and allows a comprehensive evaluation of the impact of the disease and its treatment on the physical, psychological and social aspects of the patient's life. Health-related quality of life has also been applied to measure the health status of substance use disorders. In addition, QOL-DA was developed in 1997 specifically for drug-dependent patients in China. Four measurement dimensions, social, psychological, symptomatic, and somatic, consist of 40 items, of which the social health dimension will be used as the primary outcome. Psychological, symptom, and physical dimensions will be used as secondary outcomes along with mental and physical health.

Mental health measures include subjective depression, subjective anxiety, and sleep quality. Self-rating depression scale (SDS) (50) and self-rating anxiety scale (SAS) (51) were separately used to assess subjects' depression and anxiety. SDS consists of 20 items, of which items 2, 5, 6, 11, 12, 14, 16, 17, 18, and 20 are scored in reverse, and the rest are scored positively. Score*1.25 is used to obtain the standard score. The greater the standard score, the more severe the depression. Similar to the SDS, the SAS also consists of 20 items (reverse scoring items: 5, 9, 13, 17, and 19) and is also assessed by a standard score. The higher the standard score, the more anxious the subject. Pittsburgh Sleep Quality Index (PSQI) (52) is used to assess sleep quality. It consists of 19 individual assessment items and is divided into seven components: sleep quality, sleep onset time, sleep time, sleep efficiency, sleep disorders, hypnotic drugs, and daytime dysfunction (53).

The test of physical health includes heart rate, blood pressure, vital capacity, waist-to-hip ratio (WHR) (waist and hip circumference), body mass index (BMI) (height and weight), grip, vertical jump, sit-and-reach, 50-m running, and reaction time. The test equipment adopts the national sports equipment (heart rate and blood pressure machine, spirometer, soft ruler, grip strength device, longitudinal jumping device, sit-and-reach device, reaction time measuring device). The general administration specifies the equipment and strictly follows the physical test standards.

Outcome measurements were scheduled the day before and after the experimental intervention and were measured by professional researchers at the Chengdu Sport University.

Statistical methods

Data were analyzed by two independent researchers, and all statistical analyses were performed using IBM SPSS for Windows 26.0. Data are presented as mean (standard deviation, SD), median (interquartile range, IQR), or count (%). Differences in clinical baseline characteristics and outcome measures between the two groups of participants were measured using the chi-square test of homogeneity (categorical variables), independent samples *t*-tests (normally distributed continuous variables), and non-parametric independent samples *t*-tests (non-normally distributed continuous variable). Outcome parameters for social, physical, and mental health were assessed using 2 (group: exercise and control) × 2 (time: pre-test and post-test) repeated measures ANOVA. When outcomes with significant interaction, examine by analyzing the simple effects, otherwise consider the main effects. Statistical significance was established at $P < 0.05$.

Results

Baseline characteristics of participants

The demographic data showed no statistically significant difference in age, height, weight, BMI, work status, marital status, education level, years of drug use, average dose and frequency of MA between subjects in groups of exercise and control ($P > 0.05$) (Table 1).

TABLE 1 Baseline characteristics of participants.

Characteristic	Exercise group ($n = 30$)	Control group ($n = 30$)	*P*-value
Mean age (SD), y	31.30 (3.86)	29.50 (4.59)	0.10
Mean height (SD), cm	167.82 (4.93)	170.02 (4.12)	0.07
Mean body weight (SD), kg	67.54 (7.67)	69.08 (6.77)	0.42
Mean BMI (IQR), kg/m^{2}[a]	24.22 (22.31, 25.16)	22.74 (22.25, 25.76)	0.66
Occupation, n (%)			0.61
Employed/Self-employed	15 (50)	17 (57)	
Unemployed	15 (50)	13 (43)	
Marital status, n (%)			0.50
Married	9 (30)	8 (27)	
Single	14 (47)	18 (60)	
Divorced	7 (23)	4 (13)	
Education (IQR)[b]	2 (1, 3)	2 (1,3)	0.50
Years of drug use (IQR)[c]	4 (3, 4)	4 (3, 4)	0.57
Average dose of drug use (IQR)[d]	3 (2, 3)	2 (2, 3)	0.09
Frequency of drug use (IQR)[e]	2 (1, 3)	2 (1, 3)	0.79

Data were presented as the mean ± (SD), median (IQR), or count (%).
[a]BMI = body mass index; height (m)/body weight $(kg)^2$.
[b]Unit for Education: 1 = primary school, educated for 6 years; 2 = junior high school, educated for 9 years; 3 = senior high school, educated for 12 years; 4 = college, educated for 16 years.
[c]Years of drug use are defined as from the time of the first drug use to the last drug use: 1 = less than 1 year, 2 = 1–3 years, 3 = 4–9 years, 4 = 10–15 years, and 5 = more than 15 years.
[d]Average dose of drug use was obtained through subject recalls or exchanges with drug rehabilitation authorities: 1 = less than 0.1 g at a time, 2 = 0.1–0.3 g at a time, 3 = 0.1–1.0 g at a time, 4 = more than 1.0 g at a time.[e]Frequency of drug use: 1 = once or less per week; 2 = 2–5 times a week; 3 = once a day or more.

Changes in the social health of mA-dependent individuals after exercise intervention

The results showed a strong statistically significant trend in the time and group interaction effect for social health ($F_{(1, 29)} = 4.17$, $P = 0.05$, $\eta^2 = 0.126$). Based on this result, we then conducted a simple effects analysis and found that in the exercise group, the post-intervention significantly increased compared to the pre-intervention ($F_{(1, 29)} = 24.94$, $P < 0.01$, $\eta^2 = 0.462$). And in the control group, there was no statistical difference before and after the intervention ($F_{(1, 29)} = 2.73$, $P = 0.11$, $\eta^2 = 0.086$). In addition, the scores on the post-test of the exercise group were also higher than those on the post-test of the control group and were statistically different ($F_{(1, 29)} = 10.49$, $P < 0.01$, $\eta^2 = 0.266$) (Figure 2 and Table 2).

Changes in the mental health of mA-dependent individuals after exercise intervention

The results showed that there was a time and group interaction effect for QOL-DA Psychology ($F_{(1, 29)} = 4.80$, $P < 0.05$, $\eta^2 = 0.142$), SAS ($F_{(1, 29)} = 20.85$, $P < 0.01$, $\eta^2 = 0.418$), SDS($F_{(1, 29)} = 58.67$, $P < 0.01$, $\eta^2 = 0.669$), and PSQI ($F_{(1, 29)} = 12.88$, $P < 0.01$, $\eta^2 = 0.308$). Further simple effects analysis revealed that in the exercise group, there were statistically significant differences between scores for each outcome before and after the intervention [QOL-DA Psychology: ($F_{(1, 29)} = 7.01$, $P < 0.05$, $\eta^2 = 0.195$); SAS: ($F_{(1, 29)} = 72.38$, $P < 0.01$, $\eta^2 = 0.714$; SDS): ($F_{(1, 29)} = 104.30$, $P < 0.01$, $\eta^2 = 0.782$; PSQI): ($F_{(1, 29)} = 20.90$, $P < 0.01$, $\eta^2 = 0.418$)], and the effects were focused on the post-intervention period. In the control group, the

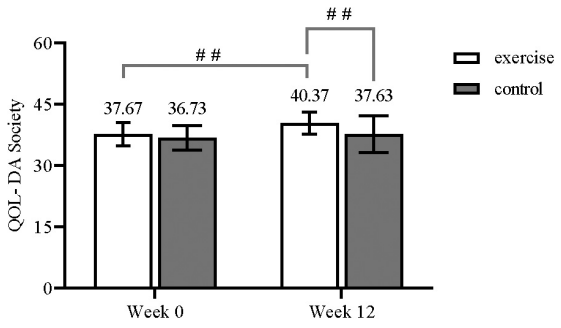

FIGURE 2
QOL-DA society in each group (## Displayed as $P<0.01$).

post-intervention SAS scores were more severe and statistically different ($F_{(1,\ 29)} = 4.76$, $P < 0.05$, $\eta^2 = 0.141$). In addition, the remaining three indicators were not statistically different before and after the intervention (QOL-DA Psychology: $F_{(1,\ 29)} = 0.001$, $P = 0.97$, $\eta^2 < 0.001$; SDS: $F_{(1,\ 29)} = 0.18$, $P = 0.68$, $\eta^2 = 0.006$); PSQI: ($F_{(1,\ 29)} = 1.40$, $P = 0.25$, $\eta^2 = 0.046$). Also, after the intervention, the QOL-DA Psychology scores of the exercise group were significantly higher than those of the control group ($F_{(1,\ 29)} = 19.98$, $P < 0.01$, $\eta^2 = 0.408$), while the SDS, SAS and PSQI scores were lower than those of the control group [SAS: ($F_{(1,\ 29)} = 59.59$, $P < 0.01$, $\eta^2 = 0.673$); SDS: ($F_{(1,\ 29)} = 91.43$, $P < 0.01$, $\eta^2 = 0.759$); PSQI: ($F_{(1,\ 29)} = 27.96$, $P < 0.01$, $\eta^2 = 0.491$)] (Table 3).

Changes in the physical health of mA-dependent individuals after exercise intervention

The results showed a time and group interaction for five physical health outcomes, including QOL-DA Symptom ($F_{(1,\ 29)} = 47.54$, $P < 0.01$, $\eta^2 = 0.621$), QOL-DA Physiology ($F_{(1,\ 29)} = 17.857$, $P < 0.01$, $\eta^2 = 0.381$), vertical jump ($F_{(1,\ 29)} = 8.82$, $P < 0.01$, $\eta^2 = 0.233$), sit-and-reach ($F_{(1,\ 29)} = 12.42$, $P < 0.01$, $\eta^2 = 0.30$), 50-m running ($F_{(1,\ 29)} = 11.87$, $P < 0.01$, $\eta^2 = 0.290$). A simple effects analysis of these outcomes found that in the exercise group, QOL-DA Symptom ($F_{(1,\ 29)} = 8.61$, $P < 0.01$, $\eta^2 = 0.229$), vertical jump ($F_{(1,\ 29)} = 20.38$, $P < 0.01$, $\eta^2 = 0.413$) and sit-and-reach ($F_{(1,\ 29)} = 5.78$, $P < 0.05$, $\eta^2 = 0.166$) were statistically different before and after the intervention. In contrast, QOL-DA Physiology ($F_{(1,\ 29)} = 0.18$, $P = 0.68$, $\eta^2 = 0.006$) and 50-m running ($F_{(1,\ 29)} = 0.61$, $P = 0.44$, $\eta^2 = 0.020$) were not statistically different before and after the intervention. Vertical jump ($F_{(1,\ 29)} = 0.13$, $P = 0.721$, $\eta^2 = 0.004$) in the control group was not statistically different, whereas QOL-DA Symptom ($F_{(1,\ 29)} = 49.66$, $P < 0.01$, $\eta^2 = 0.631$), QOL-DA Physiology ($F_{(1,\ 29)} = 43.21$, $P < 0.01$, $\eta^2 = 0.598$), sit-and-reach ($F_{(1,\ 29)} = 6.06$, $P < 0.05$, $\eta^2 = 0.173$) and 50-meter running ($F_{(1,\ 29)} = 12.19$, $P < 0.05$, $\eta^2 = 0.296$) were statistically different. In addition, QOL-DA Physiology ($F_{(1,\ 29)} = 22.80$, $P < 0.01$, $\eta^2 = 0.440$), QOL-DA Symptom ($F_{(1,\ 29)} = 32.78$, $P < 0.01$, $\eta^2 = 0.531$), vertical jump ($F_{(1,\ 29)} = 93.41$, $P < 0.01$, $\eta^2 = 0.763$), sit-and-reach ($F_{(1,\ 29)} = 8.68$, $P < 0.01$, $\eta^2 = 0.230$), and 50-meter running ($F_{(1,\ 29)} = 228.85$, $P < 0.01$, $\eta^2 = 0.890$) were significantly higher in the exercise group than in the control group after the intervention.

Within-group factors after 12 weeks of exercise intervention were statistically different in heart rate ($F_{(1,\ 29)} = 27.92$, $P < 0.01$, $\eta^2 = 0.490$), systolic blood pressure ($F_{(1,\ 29)} = 8.59$, $P < 0.01$, $\eta^2 = 0.228$), vital capacity ($F_{(1,\ 29)} = 7.29$, $P < 0.05$, $\eta^2 = 0.201$), grip ($F_{(1,\ 29)} = 120.80$, $P < 0.01$, $\eta^2 = 0.806$), and reaction time ($F_{(1,\ 29)} = 58.08$, $P < 0.01$, $\eta^2 = 0.667$). Statistical differences were found in systolic blood pressure ($F_{(1,\ 29)} = 5.72$, $P < 0.05$, $\eta^2 = 0.165$) and WHR ($F_{(1,\ 29)} = 6.73$, $P < 0.05$, $\eta^2 = 0.188$) among the between-group factors (Table 4).

Discussion

Clinical symptoms of MA abuse include social health problems caused by reduced social adaptation (6, 54). Mental health problems are caused by depression, anxiety (23), and less sleep quality (55). Physical health problems are caused by motor dysfunction (10, 56) and impaired cardiovascular function (5). The pain caused by these complex and varied symptoms can lead to uncontrollable drug relapse (19, 57), forming a vicious circle. In this study, we looked at the complete health status of MA dependents and focused on their social health indicators. This

TABLE 2 Primary outcomes: Social health.

Outcome	Exercise group ($n = 30$)		Control group ($n = 30$)		Within group *F*-value	Between group *F*-value	Time*group interaction *F*-value
	Week 0	Week 12	Week 0	Week 12			
QOL-DA Society	37.67 (2.88)	40.37 (2.75)	36.73 (3.02)	37.63 (4.50)	32.29##	18.79##	4.17

Data were analyzed with repeated measures ANOVA and presented as the mean ± (SD).
Displayed as $P<0.01$.

TABLE 3 Secondary outcomes: Mental health.

Outcome	Exercise group (n = 30)		Control group (n = 30)		Within group F-value	Between group F-value	Time*group interaction F-value
	Week 0	Week 12	Week 0	Week 12			
QOL-DA Psychology	37.77 (3.95)	40.20 (3.24)	37.03 (5.40)	37.07 (5.00)	3.05	7.26#	4.80#
SAS[a]	44.43 (7.65)	31.77 (3.89)	45.77 (5.64)	42.13 (6.24)	43.80##	36.02##	20.85##
SDS[b]	53.20 (5.12)	39.37 (6.09)	54.80 (8.95)	54.07 (6.12)	31.42##	77.82##	58.67##
PSQI[c]	6.83 (2.36)	4.57 (1.38)	6.27 (2.08)	6.83 (1.53)	8.84##	4.25#	12.88##

Data were analyzed with repeated measures ANOVA and presented as the mean ± (SD).
#Displayed as $P<0.05$.
##Displayed as $P<0.01$.
[a]SAS = Self-rating anxiety scale.
[b]SDS = Self-rating depression scale.
[c]PSQI = Pittsburgh sleep quality index.

TABLE 4 Secondary outcomes: Physical health.

Outcome	Exercise group (n = 30)		Control group (n = 30)		Within group F-value	Between group F-value	Time*group interaction F-value
	Week 0	Week 12	Week 0	Week 12			
QOL-DA Symptom	49.77 (3.57)	52.27 (3.43)	51.40 (1.89)	46.40 (4.35)	4.90#	8.17##	47.54##
QOL-DA Physiology	36.47 (3.48)	36.13 (3.12)	37.13 (2.93)	31.80 (3.75)	27.37##	7.63##	17.86##
Heart Rate (bpm)	82.37 (12.92)	73.13 (11.68)	79.33 (11.29)	73.17 (10.62)	27.92##	0.32	0.38
Systolic Blood Pressure (mmHg)	124.33 (8.40)	115.03 (16.07)	125.53 (10.85)	123.03 (11.06)	8.59##	5.72#	1.98
Diastolic Blood Pressure (mmHg)	75.77 (8.20)	73.13 (14.21)	75.27 (7.33)	76.33 (7.37)	0.17	0.69	1.11
Vital Capacity (ml)	3442.60 (554.20)	3669.10 (504.88)	3502.50 (644.60)	3762.20 (485.93)	7.29#	0.62	0.03
WHR[a]	0.88 (0.06)	0.86 (0.05)	0.89 (0.05)	0.89 (0.04)	2.32	6.73#	1.25
BMI[b]	23.97 (2.41)	24.14 (2.35)	23.93 (2.54)	24.08 (2.78)	2.09	0.02	0.01
Grip (kg)	38.22 (6.93)	47.96 (7.82)	37.72 (7.99)	45.86 (5.16)	120.80##	2.54	1.25
Vertical Jump (cm)	35.15 (7.27)	39.83 (5.75)	35.41 (7.66)	34.82 (4.12)	3.72	4.94#	8.82##
Sit-and-Reach (cm)	11.22 (9.62)	14.18 (6.96)	11.87 (6.44)	9.84 (4.67)	0.37	1.19	12.42##
50-Meter Running (s)	8.67 (0.64)	8.55 (0.65)	8.44 (0.58)	8.93 (0.54)	2.74	0.70	11.87##
Reaction Time (s)	0.54 (0.09)	0.43 (0.04)	0.55 (0.10)	0.48 (0.05)	58.08##	2.34	3.85

Data were analyzed with repeated measures ANOVA and presented as the mean ± (SD).
#Displayed as $P<0.05$.
##Displayed as $P<0.01$.
[a]WHR = Waist-to-Hip Ratio; waist (cm)/hip (cm).
[b]BMI = Body Mass Index; body weight (kg)/height $(m)^2$.

study provides evidence on the impact of a 12-week moderate-to-intensity aerobic exercise intervention on the social, physical, and mental health of MA dependents. Statistically, subjects in the exercise group had better social, mental, and physical health than those in the usual care group, and no adverse effects were reported throughout the trial.

As found in previous studies, in the area of drug abuse, adverse social activities induce a strong motivation to continue seeking drugs (58, 59) and enhance drug relapse (60, 61). Individuals with concurrent social health problems have a higher risk of death (62). While MA abusers may have persistently high levels of psychological distress and hostility that are detrimental to their social interactions, health concerns in the social sphere of MA dependents are worthwhile (63). However, studies on exercise therapy for the social health of MA dependents are relatively few. One study found that low to moderate intensity physical and mental exercise for 3 months could positively impact social functioning in individuals with substance use disorders (43). In addition, acute exercise interventions, either 1 h of aerobic exercise alone or 1 h of strength combined with aerobic exercise, can improve social health in amphetamine addicts (64). Their findings are consistent with the present study's; that is, physical exercise improves the social health status of MA dependents, which may be because exercise intervention repairs damaged brain regions or nervous systems in MA abusers (32). This view that exercise can reduce addiction is widely accepted (65, 66). The functional brain regions responsible for processing social inclusion and exclusion are mainly located in the insula (67, 68), and drug abuse will directly damage the insula's neural structures. At the same time, MA abuse leads to an imbalance in the dopaminergic system, in which type 1 dopamine receptor signaling in the ventral tegmental area mediates complex social behavior (69) and the availability of striatal dopamine D2/3 receptors correlates with subjects. The correlation between social status and perceived social support is positive (70). As a treatment for drug addicts, physical exercise's effectiveness on social health may involve repairing or protecting neural structures such as the insula and dopamine system. (71–73), which may explain why exercise can improve the social well-being of MA-dependent individuals.

The scores of psychological symptoms, self-rating depression, self-rating anxiety, and sleep quality index in the exercise group were significantly improved after 12 weeks of exercise intervention. These results did not change in the control group, and the health scores improved over time. This is similar to a previous study that eight weeks of exercise training improved symptoms of depression and anxiety in MA-dependent individuals (39). It is worth noting that the effectiveness of exercise in improving sleep quality (74, 75), although constantly proven, is rarely mentioned in MA dependents (76). Our findings support the use of 12 weeks of moderate-intensity aerobic exercise as an effective prescription for improving mental health and enhancing sleep quality in MA-dependent individuals. In terms of physical health, the 12-week exercise intervention reduced the withdrawal symptoms of MA-dependent individuals and improved their physical function. The cardiovascular benefits were also consistent with previous studies. Exercise lowered blood pressure in MA-dependent individuals. Physical, strength, flexibility, speed, and agility quality have improved, which is consistent with previous research results (39, 77); that is, MA-dependent individuals who participate in sports will have better physical health and psychological effects (43).

The study found no adverse events during the intervention, and no subjects dropped out of the trial, suggesting that moderate-intensity aerobic exercise can be safely used in MA-dependent individuals to restore their health. And, the effectiveness of the exercise program in this study (12 weeks of moderate-intensity aerobic exercise for 1 h, 5 times per week) could inform targeted exercise prescriptions for drug-dependent individuals in future studies. However, this study still has several limitations. First, the sample size of this study is small. Second, the selected participants were all male; thus, the effect of gender could not be assessed. Finally, during the implementation period of the trial, the subjects were not banned from tobacco use, which may have potential effects on the subjects' cardiorespiratory fitness. Therefore, in future work, while expanding the sample size, more female subjects should be included in the trial research to obtain more comprehensive evidence. Despite the study limitations, the data from this study can provide preliminary evidence that exercise improves the health of MA-dependent individuals, and the overall health of special populations should be given focus.

Conclusion

This study shows that moderate-intensity aerobic exercise intervention is an effective treatment for MA-dependent individuals and that 12 weeks of intervention improved social well-being, depression, anxiety, and sleep in MA-dependent individuals. The resulting mental health also enhanced physical health, including systolic blood pressure, WHR, vertical jump, seated forward bend, 50-m run, and reaction time. Future studies should pay more attention to the overall health status of drug-dependent individuals rather than just their relapse.

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 the Ethics Committee of Chengdu Sports

University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JX and ZZ: methodology, investigation, and writing – original draft. JX and XLi: conceptualization and funding acquisition. XLi: resources, project administration, supervision, and writing – review and editing. XLia: validation and data curation. QH and TZ: visualization and formal analysis. All authors have read and agreed to the published version of the manuscript.

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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.

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Applications of technology in the assessment and treatment of cannabis use disorder

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Cannabis use and Cannabis Use Disorder (CUD) have been increasing. There are no FDA approved medications and evidence-based psychotherapy is limited by insufficient providers, serving very few patients effectively. The lack of resources for prevention and treatment of CUD has resulted in a significant gap between the need for services and access to treatment. The creation of a scalable system to prevent, screen, refer and provide treatment for a chronic, relapsing diagnosis like CUD could be achieved through the application of technology. Many studies have utilized ecological momentary assessments (EMA) in treatment seeking and non-treatment seeking cannabis users. EMA allows for repeated, intensive, longitudinal data collection *in vivo*. EMA has been studied in cannabis use and its association with affect, craving, withdrawal, other substances, impulsivity, and interpersonal behaviors. EMA has the potential to serve as a valuable monitoring tool in prevention, screening, and treatment for CUD. Research has also focused on the development of internet and application-based treatments for CUD, including a currently available prescription digital therapeutic. Treatment options have expanded to more broadly incorporate telehealth as an option for CUD treatment with broad acceptance and change in regulation following the COVID-19 pandemic. While technology has limitations, including cost, privacy concerns, and issues with engagement, it will be a necessary medium to meet societal health needs as a consequence of an ever-changing cannabis regulatory landscape. Future work should focus on improving existing platforms while ethically incorporating other functions (e.g., sensors) to optimize a public and clinical health approach to CUD.

KEYWORDS

cannabis, cannabis use disorder (CUD), technology, ecological momentary assessment, treatment, assessment

Introduction

Cannabis use disorder (CUD) is a public health problem associated with psychiatric and medical morbidity (1, 2), poor performance (3), and decreased quality of life (4). In 2020, 14.2 million people aged 12 years and older met criteria for CUD (5). Despite the large number of patients with CUD, we have limited treatments. There are no Food and Drug Administration (FDA) approved medications; however, many pharmacological

trials have been completed with some support for off-label usage of certain medications, the overall evidence to date is incomplete and does not provide definitive guidance (4, 6). Evidence-based psychotherapies are the primary intervention (7). There is a notable treatment gap for CUD, in that a minority of patients who would benefit from specialized treatment do not have access (5). Additional factors that contribute to this include stigma, poorly disseminated information regarding where to access treatment, misinformation about the abuse potential and safety of cannabis, geographic barriers and transportation limitations, a non-patient centered treatment system (e.g.: schedule based on provider not patient), limited integration and lack of referrals within the larger healthcare system, lack of insurance coverage for services, lack of perceived need for specialty care by patients and other providers, and concerns for privacy and confidentiality (8).

Simultaneously, the majority of adults living in the U.S. has access to home broadband internet (77%), and a smartphone (85%), which has been increasing year over year (9). Given this landscape, applying technology in the assessment and treatment of CUD has the potential to reach patients at scale with effective treatments by building a technology-enabled infrastructure to optimally prevent, screen, treat, and minimize the consequences of cannabis use and the development of CUD. CUD is an especially promising target for digital assessments and interventions. The chronic nature of the disorder requires a treatment paradigm that can increase patient and provider awareness through monitoring, initiate abstinence, prevent relapse, provide maintenance support, and interventions if relapse occurs to reinitiate abstinence. This model requires proactive and longitudinal assessment and treatment that is difficult to provide in traditional brick and mortar clinics. Clinical research in the application of technology to the assessment and treatment of CUD is in its incipient stages, though important work has been done demonstrating clear feasibility, acceptability, and clinical utility of many modalities. This brief review will cover research of technology in (1) the assessment of cannabis use and other key factors in CUD, (2) the treatment of CUD, (3) limitations, and (4) future directions.

Use of technology in the assessment of cannabis use and cannabis use disorder

Successful public health campaigns must appropriately screen, monitor, accurately assess, and then either prevent the development of CUD or refer for services (10). The use of technology in the form of screening assessments provided through digital platforms would be the first step in this systematic public health approach to cannabis (11). Ecological momentary assessments (EMA) can prospectively capture behavior, emotion, or cognitive functioning in close to real-time through scheduled, random, or self-initiated prompts longitudinally on a smartphone. The *in-vivo* assessment minimizes the impact of memory degradation and recall biases and provides high real-world validity (12, 13). EMA, its frequency, and duration of collection can be highly tailored to the population of interest. EMA has been shown to be clearly feasible and acceptable in individuals who use cannabis, including those with co-occurring disorders. Individuals who use cannabis or have CUD have high average completion rates of prompts of 85–86%, with lower rates of completion of ∼75% in populations with notable disability and polysubstance use (14, 15). Studies using EMA to assess individuals using cannabis or with CUD have been completed in multiple states (15). The lack of geographical limits and the increased representation from historically harder to reach groups opens the door for both national and international projects. As an example, nationally there is an opportunity to elucidate changes in health with changes in state policy related to recreational and medical cannabis legalization (15). EMA has the added clinical benefit of improving self-awareness in participants who report finding EMA "helpful" in brining attention and greater agency to their cannabis use (15, 16). EMA has been used in both treatment seeking and non-treatment seeking individuals using cannabis (16), and to assess use of multiple substances that may be related to use of cannabis, including nicotine, and alcohol, providing valuable information on the complicated nature of co-use and impact on cognitive functioning (17–19). EMA has been implemented on study provided smart phones and on participants' own phones. The former ensures equity of access and user experience; the later providing for greater generalizability for use in a real-world population.

Research has utilized EMA to assess existing policies and programs for cannabis use prevention and mental health support in addition to assessing participants' experiences with mental health and behaviors (20). EMA has demonstrated how cannabis use may mediate suicidal ideation in youth in addition to identifying that bullying and being a gender minority resulted in increased risk (20). In addition to looking at suicidal ideation and stressful experiences (e.g., bullying), multiple studies of EMA and cannabis use have explored positive and negative affect and craving as it relates to risk of use, demonstrating a mixed and inconsistent relationship, with some studies finding cannabis serves more as positive reinforcement and in other studies as a negative reinforcement with overall severity of CUD driving sharper increases in positive reinforcement and craving (16, 21, 22). Other research has assessed anxiety, craving, social factors (e.g., peers using cannabis), and withdrawal symptoms in individuals with regular cannabis use and CUD to see how they are related to cannabis cessation or continued use (23–25), finding that anxiety, craving, and environmental factors most greatly influenced use of cannabis. Other studies have assessed impulsivity and interpersonal hostility as mediators of cannabis use, finding that cannabis use increased impulsivity and hostility

(26, 27). These findings suggest that factors driving cannabis use, including affect and craving, are dynamic, transient, and variable neurobiological processes within individuals and may underlie cannabis use problems (28).

A recent study collected EMA data in adolescents while also capturing objective data from smartphones to improve data quality and enhance data fidelity including use of the smartphone camera to capture and provide photographs of participant identification to confirm eligibility, activity tracking on the phone to assess usage and screentime, accelerometer data to estimate physical activity, and the smartphone's global positioning system (GPS) to assist with geolocation and confirmation of school attendance (20). Many studies depend solely on self-report of outcomes of interest, ultimately limiting conclusions and understanding of biological and environmental factors that are not captured (29). Future studies that use EMA should build off the work done to date and combine other technologies that can also collect passive, objective data, such as can be done with the use of sensors, to capture these complex intra-individual processes in conjunction with biologics and cannabinoid testing to confirm use.

To date, no study that these authors are aware has been completed and published utilizing EMA in a clinical treatment trial for CUD as the primary outcome, though current studies are underway [(16); NCT05273567; NCT05322941]. Given that EMA has been shown to be superior to global self-report, fixed time assessment measures, and retrospective self-report, making use of EMA to assess treatment outcomes in CUD treatment trials will be valuable in improving data quality and limiting recall bias inherent to traditional primary endpoints (Timeline Followback) (30).

Use of technology in the treatment of cannabis use disorder

Clinical research, including randomized controlled trials, utilizing technological platforms in the treatment of CUD, as part of substance use disorder treatment more broadly, began in the late 1990's and early 2000's with the emergence of the first wave of digital therapeutics and coincided with a global interest and increased utilization of the internet to fulfill new functions. These internet-based programs offered an opportunity to deliver high fidelity interventions at scale (31). Clinical research of face-to-face, manualized psychotherapies for CUD, such as Motivational Interviewing, Cognitive Behavioral Therapy and Contingency Management, emerged as clearly efficacious and made use of tangible and teachable skills and behavioral theories, such as mindfulness, breathing and relaxation exercises, and reward incentives, while adhering to an educational framework that explained and practiced through homework behavioral activation, cognitive restructuring, goal-setting, and strategies for coping. These treatments translated well to online materials and internet platforms (32). Early versions of these internet-based programs for CUD and other substance use disorders, such as the Therapeutic Education System (TES) (33) and CBT4CBT (34) were delivered *via* web-pages and accessible through internet connection on computers. These treatments consistently demonstrated improvements in clinical outcomes and increased acquisition of skills for patients with substance use disorders including CUD in large, randomized, controlled trials (33, 35). Additionally, studies found that these technology-based interventions are superior to no treatment and are non-inferior to in-person psychotherapy (36–38).

The internet-based treatment programs for CUD and other substance use disorders provided the foundation for a second and current wave of technological interventions for addiction. Developing in parallel with the ecosystem allowing for internet access through smartphones and tablets, these treatments were formatted into downloadable software in the form of applications ("apps"). Apps have the benefit of interfacing with and accessing features of smartphones not typically used in desktop computers such as cameras, sensors, and location through GPS (39). They also allow for continuous communication, including when patients are not currently using the application by enabling prompts through push notifications (39). Some application functions may work offline allowing for access in the absence of an internet connection (39). Mobile applications for substance use disorders such as CUD most notably include the Food and Drug Administration (FDA)- approved prescription digital therapeutic reSET^{TM}, developed by Pear Therapeutics Inc. (US) for the treatment of substance use disorders. reSET^{TM} provides application-accessible CBT-based treatment modules. It has functions that include health education, identification of triggers, individualized strategies and skills to address cravings and high-risk situations, assessments and feedback of the patient's acquisition of therapeutic principles, and a clinician dashboard to assist in overseeing patient progress during the 12-week prescription-required program. During this time patients also monitor and report on substance use, cravings, or triggers, while the healthcare provided can input urine toxicology results and record current medications. This comprehensive prescription digital therapeutic has been shown to effectively support abstinence and reduce the risk of relapse. reSET^{TM} was designed to be used in conjunction with in-person sessions with prescribers in the treatment of substance use disorders including CUD, allowing for a hybrid application of technology. This prescription digital therapeutic requires a prescription by a clinician to access and download the platform. Unlike health and wellness applications that patients can access directly, prescription digital therapeutics are rigorously evaluated for safety and effectiveness in randomized controlled trials and must meet authorization standards by the U.S. Food and Drug Administration (FDA). They are subject to post-marketing requirements that are similar to regulated pharmaceuticals.

These FDA approved software treatment products also include stringent security and privacy controls which is highly important given the nature of the health information collected (40).

Web-based programs, such as TES and CBT4CBT, and prescription digital therapeutics like reSET^{TM}, are treatments that transdiagnostically address substance use disorders including CUD. Multiple rigorous randomized, controlled trials have also been completed using self-guided (41, 42), clinician guided, or chat-supported (43, 44) web-based treatment programs specific to CUD. These studies found internet-based programs to be effective alternatives for lower severity and less complicated patients or potentially helpful supplemental resources in reducing cannabis use and symptoms if not adequate as stand-alone treatments for abstinence.

The use of telehealth for the treatment of CUD has never been more important or more widely utilized. Telehealth is the remote delivery of healthcare using telecommunications technology, most commonly by video conferencing (45). Prior to the COVID-19 pandemic, there were notable financial, legal, and regulatory barriers that prevented widespread adoption of delivering treatment for substance use disorders remotely facilitated by technology (46). In March 2020, utilization of telehealth in the US increased 154% in <1 month (47), fueled by policy changes that improved provider payments for telehealth, permitted interstate treatment, authorized multiple types of providers to perform telehealth services, reduced or waived cost-sharing for patients, allowed for virtual visits to be conducted from the patient's home, rather than a clinic, and granted widespread permission to federally qualified health centers or rural health clinics to offer telehealth services (48). Prescribers quickly adapted to the new environment in utilizing home-based telehealth as a primary means of providing treatment. This means of providing treatment is likely to continue to be a mainstay option for patients to access specialized treatment for CUD, as both providers and patients find it satisfying and convenient (49, 50).

Limitations and considerations

While the assessment and treatment of CUD with technology brings many promises, there are some limitations and considerations that will need to be addressed. Privacy, anonymity when possible, and data sovereignty at the level of the individual must be primary goals when considering the use of technology and its ability to prevent and treat CUD. Confidentiality must be protected through the use of passwords, data de -identification, and encryption. Informed consent should be clear and explicitly presented with regards to actively and passively collected data. Options to drop-out and stop data acquisition should be presented and easily fulfilled if desired. Research and treatment with technology will need to ethically balance participant confidentiality with data quality and reach of scientific understanding (51). Internet and smartphone inequity is an additional barrier, particularly for individuals who are older, have unstable housing, and live in countries with inadequate infrastructure to support technology dependent services, such as in developing nations and more rural areas (11, 52).

Despite the availability of existing applications and a commercially available prescription digital therapeutic, the overall impact on assessing and treating CUD is low. Factors contributing to low penetration of technological tools for CUD include lack of awareness of these mobile health treatments by providers and patients, limited adoption by patients and providers due to factors outlined above, and low patient engagement, usage, and adherence, particularly over time (53). In the case of prescription digital therapeutics, prescribers may not be familiar, comfortable, or competent in deploying these therapeutics. Prescribing a non-medication treatment to a patient may be novel for many clinicians since it is operationally distinct from referring a patient for psychotherapy. Most clinicians are not trained in the use of technology for treatment, outside e-prescribing and documentation in electronic health records, which may slow adoption of new modalities and subsequent uptake by patients. Healthcare and psychology graduate school programs should add training in digital technologies for CUD to facilitate patient access.

Engagement and completion rates have been low to moderate with digital interventions for CUD. Engagement may be improved by integrating content, language, interfaces, delivery systems and rewards that are more salient and specific to the individual. For example, applications for adolescents should include elements that are more relevant to this age group (54). Design of these interventions must take into account key, qualitative differences in the experience of the patient and clinician (55). Research should consider incorporating social media and gaming that could be applied to CUD assessments and interventions to improve engagement, particularly in youth.

Finally, initial costs of purchasing, learning, and implementing new digital assessments and treatments takes time and financial investment. There are limited codes for payer reimbursement for reviewing a technological assessment or utilizing a prescription digital therapeutic. The current system will need to adapt to provide compensation and coverage for these services to further adoption.

Future directions

Future research, screening, prevention, and treatment for CUD should continue to build upon the strong work completed today. The use of EMA should expand to build toward not just in-depth assessment but ecological momentary interventions (EMI) that can be specific and appropriate (56, 57). Machine learning has already been able to predict the

folding process of 200+ million proteins based on their amino acid sequencing (58). Applying machine learning to predict risk for the development of CUD or provide informed interventions to prevent engagement in cannabis use in real-time while simultaneously providing access to digital services (59, 60).

Internationally there have been increases in cannabis consumption across ages (61). Assessments and treatments delivered through technological platforms can easily be translated into different languages. Mobile health interventions targeting cannabis have been applied to helping pregnant people (62), individuals with comorbid psychiatric disorders like psychosis (63), students in schools (20), incarcerated offenders (64), co-occurring chronic pain and opioid use (15), individuals with cannabis and other substance co-use (18, 65), and racially diverse populations (66). Future work can modify existing applications or build new, custom platforms to improve and expand the reach of these assessments and treatments to support diverse populations through socially and culturally competent means. Targeted interventions can prioritize at risk groups. While some interventions to have allowed for a patient-clinician interface, future versions should expand the support network to include therapists, family-members, peers, and other stakeholders to provide input and resources toward the prevention or treatment of cannabis use and CUD.

As the field matures, we anticipate that technology will be ubiquitous in research and clinical care of CUD. While work to date has focused on patients or providers actively inputting their observations, subjective accounts may be best utilized in a limited fashion. Ideal characteristics of digital tools of a chronic, relapsing disorder like CUD allow for continuous monitoring, are unobtrusive and create a lower user burden, and allow for remote acquisition of data in a naturalistic setting. Future work should focus on these goals and optimize for them by expanding into other areas such as social media, augmented and virtual reality, and sensors.

Conclusions

Effective applications of technology have the potential to address the gap in treatment and prevent the development of CUD in high-risk groups. EMA and web and application-based treatments have been studied most extensively and have the greatest data supporting their feasibility, acceptability, and efficacy for CUD, culminating in an FDA approved prescription digital therapeutic. Current clinical treatment should utilize these tools and future research should expand to explore the use of other technology for CUD while improving existing applications. As with any new technology, attention must be given to its limitations to thoughtfully and effectively derive the greatest benefit.

Author contributions

CB conceptualized the paper and wrote the first draft. CB and FL discussed approach and outline. FL reviewed and provided edits and revisions. All authors incorporated journal-provided reviews and edits.

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Conflict of interest

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

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Negative symptoms in alcohol use disorder: A pilot study applying the two-factor model of negative symptoms to patients with alcohol use disorder

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Background and aims: Alcohol Use Disorder (AUD) is characterized by a reduction in goal-directed behavior, with alcohol use taking precedence over other areas of life. These features in AUD resemble negative symptoms in schizophrenia, especially the reduction in motivation and pleasure (MAP). Given the clinical similarities of negative symptoms across diagnostic categories, it comes as a surprise that there are few investigations on negative symptoms in alcohol and other substance use disorders. To our knowledge, our study is the first to assess negative symptoms in AUD based on a two-factorial approach, and to investigate the interrelation of these dimensions with the severity of AUD, and alcohol craving.

Materials and methods: We examined a sample of 42 patients with AUD at the Psychiatric University Hospital in Zurich. Participants provided self-report and interview-based measures of the severity of AUD, negative symptoms, and alcohol craving. Finally, we used data from the electronic health records of the patients.

Results: Patients with AUD show negative symptoms to a similar extent as patients with schizophrenia or bipolar disorder. We found a positive correlation between the extent of impairment within the MAP factor and overall severity of AUD. Furthermore, MAP negative symptoms were correlated with alcohol craving. In a linear regression, negative symptoms predicted alcohol craving whereas depression did not.

Summary: Negative symptoms as conceptualized for schizophrenia are prevalent in patients with AUD and associated with the severity of AUD. More specifically, severity of AUD correlates with diminished motivation

and pleasure, highlighting the importance of disturbances in motivational functions in AUD. This is further supported by the correlation between negative symptoms and craving, a hallmark of AUD. Taken together, our findings suggest that negative symptoms might be a highly relevant but hitherto often neglected therapeutic target in AUD.

KEYWORDS

alcohol use disorder, negative symptoms, anhedonia, craving, substance use disorder, addiction, motivation and pleasure

Introduction

Alcohol is extensively used worldwide (1). Besides its desired acute effects, like euphoria and anxiolysis, excessive alcohol use has negative health consequences. Chronic alcohol use is among the leading causes for premature death and contributes to the global burden of neuropsychiatric and somatic diseases with enormous direct and indirect economic costs (2, 3). An estimated 4.3% of the Swiss population aged over 15 years show a chronic pattern of risky alcohol consumption (4). Lifetime prevalence of alcohol use disorder (AUD) is estimated to be 8.6% (1). Of those suffering from AUD, over 80% do not receive adequate treatment (5). After treatment, relapse is common (6). Monahan and Finney found abstinence rates of only 43% after treatment (7). Even after achieving long-term abstinence, there seems to be an annual relapse rate of 3% (8).

Among the features of AUD are substance craving, and a shift in goal-directed behavior toward the obtainment and use of alcohol (9). The upcoming ICD-11 considers this shift in behavior as one of the three main features that characterize alcohol dependence: "*Substance use becomes an increasing priority in life such that its use takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or personal care. Substance use takes an increasingly central role in the person's life and relegates other areas of life to the periphery. . .*" (10).

During the course of AUD and other substance use disorders (SUDs), substance use progresses from an initially voluntary to a more habitual and finally obsessive-compulsive stage (11). The brain's reward system is profoundly dysregulated in addictive disorders and plays a key role in the development and maintenance of addiction (12–14). The adaptations affect different neurotransmitter systems including dopamine (15–17), glutamate (18–20), and GABA (21). In animal addiction models, different motivational states within the cycle of substance-seeking are paralleled by distinct oscillations in synaptic strength within the pathway between the prefrontal cortex and the nucleus accumbens (22), two important hubs for reward processing (23). Also in human imaging studies, functioning of those regions have been significantly altered in individuals with SUDs, indicated by increased activity in response to substance-related cues (24–26), which is linked to increased substance craving (27, 28). In contrast, the prefrontal cortex, and the nucleus accumbens show reduced responsiveness toward naturally rewarding cues such as social stimuli and monetary reinforcers (29–31).

In schizophrenia, the symptoms nowadays termed negative symptoms (32) have been considered a hallmark of the disease since Kraepelin and Bleuler (33, 34). As defined by the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) Consensus Statement, negative symptoms include the following domains: blunted affect, alogia, asociality, anhedonia, and avolition (35). These domains can be summarized in two factors; the first, "motivation and pleasure" (MAP, sometimes referred to as "apathy"), consists of the domains asociality, anhedonia, and avolition. (36–38). The second factor, "diminished expression" (DIM), includes the domains blunted affect and alogia. The neurobiological basis for deficits in the motivation and pleasure domain is still debated; however, areas involved in reward prediction, like the ventral striatum, may be central (39). Negative symptoms are also present in patients with schizophrenia and comorbid SUD (40–42).

Anhedonia, which is defined as a reduced experience of pleasure is regarded as a core feature of schizophrenia and is also a key symptom of depression and common in various other psychiatric conditions (43). Recent research has shown that patients with schizophrenia, however, often report a normal or even elevated hedonic response to reward (44, 45). Their ability to *anticipate* pleasure in future reward, on the other hand, is diminished (46, 47). These patients show a social performance rather than a hedonic deficit (37). This has led to a distinction between anticipatory ("wanting") and consummatory ("liking") anhedonia (48). Interestingly, this distinction was first conceptualized in SUDs (17).

In SUDs, anhedonia has been regarded as part of the (prolonged) withdrawal symptomatology (49–54), a possible

risk factor for relapse (55, 56) and as crucial for treatment outcome (57–59). Nguyen et al. found that anhedonia correlated with relapse rates in AUD (60). In studies in patients with cocaine use disorder, anhedonia had a negative impact on the effectiveness of contingency management treatment (57, 61, 62). A study by Huhn et al. in patients recovering from opioid use disorder showed a reduced activation of the prefrontal cortex for natural reward that in association with the extent of anhedonia (58). Janiri and colleagues found a significant correlation between anhedonia and substance craving (63). Furthermore, an anhedonic trait has been discussed as a risk factor in the development of addiction (64–66). For a systematic review of the literature on anhedonia in substance use disorders, see Garfield et al. (67).

The other two domains that comprise the motivation and pleasure factor of negative symptoms are asociality and avolition (35). Asociality can be defined as a lack of motivation to engage in social interaction. Avolition is a general reduction in the ability to initiate goal-directed behavior. In summary, the factor "motivation and pleasure" describes different aspects of an inability to anticipate and engage in behaviors usually regarded as pleasurable or otherwise rewarding. This factor shows a great degree of similarity with two of the diagnostic criteria of AUD in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (9):

- A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
- Important social, occupational, or recreational activities are given up or reduced because of alcohol use.

The second factor, "diminished expression," signifies the reduced capability to experience and/or express emotions. The subdimension "blunted affect" refers to the subjective experience and non-verbal expression of emotions, whereas "alogia" means poverty of verbal expression (35).

Whereas anhedonia, in particular trait and consummatory anhedonia, has been studied in populations with SUDs, to our knowledge no study has yet applied a more extended model of negative symptoms to AUD. Considering the similarities between negative symptoms in schizophrenia and some of the clinical features in AUD, it seems plausible to examine whether the full spectrum of negative symptoms—not just consummatory anhedonia—can be found in patients with AUD (68).

In this pilot study, we examined the two-factorial model of negative symptoms in a sample of patients with AUD. We further investigated whether MAP or DIM are specifically related to overall severity of AUD and craving.

Materials and methods

Study setting

This cross-sectional study was conducted at the Psychiatric University Hospital Zurich, Switzerland. Clinical interviews and assessments took place from July 2020 until January 2021.

The studies involving human participants were reviewed and approved by Cantonal Ethics Committee, Zurich, Switzerland. The participants provided their written informed consent to participant in this study.

Sample

Prior to the start of the study, all therapists at the Center for Addictive Disorders and the Center for Integrative Psychiatry at the Psychiatric University Hospital Zurich (Psychiatrische Universitätsklinik Zürich, PUK) were asked to check for eligible patients.

Inclusion criteria for study participation were as follows: diagnosis of AUD regardless of the stage of the disorder (e.g., abstinent, currently addicted, relapsed), age between 18 and 65 years, ability to provide written informed consent and to communicate in German. Exclusion criteria were a current or former diagnosis of schizophrenia or bipolar disorder, a diagnosis of severe neurological disorders or other somatic disorders which would impact the ability to participate. All other comorbidities were allowed.

Sixty-three eligible patients were reported to us by their respective therapist, 14 of whom did not respond to our contact *via* telephone, six refused to participate, and one patient did not meet the inclusion criteria. Therefore, the final sample consisted of 42 patients in total, 33 of whom were outpatients and nine were inpatients. Ten participants have been abstinent from alcohol for a miminum of 30 days prior to their inclusion in the study. For details, see **Table 1**.

Measures

Clinical interviews and questionnaires

The Mini International Neuropsychiatric Interview (MINI) is a structured diagnostic interview consisting of up to 120 questions that allows for diagnosing axis-I disorders of the DSM-IV as well as suicidality (69). It is a structured, easy to conduct interview requiring only minimal training.

The Center for Epidemiological Studies Depression Scale (CES-D) in its German Version (Allgemeine Depressionsskala, ADS-L) was used to assess depressive symptoms (70, 71). The ADS-L is a 20-item self-report questionnaire, items are rated on a four-point Likert scale from 0 (rarely/not at all) to 4 (most of

TABLE 1 Demographic and sample characteristics.

Characteristic	M	*N*	%	SD	Range
Female		18	42.9		
Age (years)	43.74			10.61	22–65
Inpatients		9	21.4		
Number of inpatients stays	5.19			7.14	0–34
No inpatient stays		7	16.7		
1–3 inpatient stays		20	47.6		
4–10 inpatient stays		6	14.3		
More than 10		9	21.4		
Suicidality (light or severe)		15	35.7		
Diagnoses					
Major depression		12	28.6		
No comorbidities		8	19.0		
One comorbid disorder		13	31.0		
More than one comorbidity besides AUD		20	47.6		
PSP score (psychosocial functioning)	2.64			0.70	1.3–4.5
Cognitive Variables					
Digit Symbol Substituion Test (*n* in 120 s)	57.72			14.66	14–90
Letter-Number Sequencing (longest letter-number sequence)	8.98			2.93	3–14

Inpatients stays refer to the stays at PUK. Diagnoses were collected with the MINI and psychosocial functioning with the Personal and Social Performance Scale (PSP). Cognitive functioning was measured with the Digit Symbol Substitution Test (DSST) and the Letter-Number Sequencing. The MINI data is missing for one participant.

the time). A score of 23 or higher indicates clinically relevant depressive symptoms.

The Calgary Depression Scale for Schizophrenic Patients (CDSS) was developed to assess depressive symptoms in patients with schizophrenia in distinction from negative and extrapyramidal symptoms (72, 73). It has been validated in patients with major depressive disorder (74) as well as healthy subjects (75). It is a semi-structured interview consisting of nine items. The first eight items are open-ended questions; the interviewer rates participants' answers on a four-point Likert scale ranging from severe to absent. For the last item, the interviewer rates the extent of depressive symptoms observed during the interview. A cut-off score of six allows for identification of depression in patients with schizophrenia.

Substance use was recorded using a Timeline Followback (TLFB) form. Any alcohol use was defined as drinking alcohol on a minimum of 3 days per week. For the last 7 days, the number of drinking days and the number of alcoholic beverages per drinking day were recorded. Currently abstinent participants were asked to name the number of alcoholic beverages usually consumed in 1 week. Harmful use of alcohol was defined as drinking more than one standard drink per day for women and two standard drinks for men, respectively.

The German Version of the Obsessive Compulsive Drinking Scale (OCDS-G) (76) is a self-assessment scale consisting of 18 questions. It captures cognitive aspects such as preoccupation with alcohol consumption, the amount of alcohol consumed typically, the subjective extent of substance craving, psychosocial impairments following alcohol consumption and the feeling of control over alcohol consumption. It also includes three visual analog scales on which participants rate the extent of craving.

The Brief Negative Symptoms Scale (BNSS) is a semi-structured 13-item interview on six domains, namely the five domains of negative symptoms defined by the NIMH MATRICS Consensus Definition Conference plus lack of normal distress as a sixth domain (77). These domains are assigned to two dimensions, diminished expression (DIM) and motivation and pleasure (MAP). The MAP dimension consists of the three domains, anhedonia, avolition and asociality, whereas the two domains, affective flattening and alogia (poverty of speech), form the DIM dimension. The interviewer asks open-ended questions regarding social and other activities as well as stressful events and rates the extent of impairment on a seven-point Likert scale.

The Self Evaluation of Negative Symptoms (SNS) is a 20-item questionnaire for the self-assessment of the five domains of negative symptoms blunted affect, alogia, social withdrawal, anhedonia, and avolition (78). Each item is rated on a 3-point Likert scale. The sum of all 20 items forms a total score, ranging from 0 to 40 corresponding to the severity of negative symptoms. A score below seven is considered non-pathological.

The Temporal Experience of Pleasure (TEPS) (79) measures anticipatory and consummatory hedonic capacity and consists of 18 items on a 6-point Likert scale. The average of the score of each item forms the total score with higher scores indicating higher hedonic capacity and lower scores indicating higher anhedonia, respectively. It has been tested in a sample with opioid-dependent participants (80).

To assess cognitive functioning, we used the Digit Symbol Substitution Test (DSST) and Letter-Number Sequencing, two subtests of the Wechsler Adult Intelligence Scale(81).

Therapist-rated questionnaires

The Rapid Addiction Profile (RAP) is rated by the therapist on a 4-point scale (82). It covers five dimensions: somatic level, psychiatric level, motivation level, crisis level and resource level. The total score ranges from 0 to 20 points, with higher scores indicating greater severity of AUD.

The Personal and Social Performance Scale (PSP) (83) is rated by the participants' therapists to assess the level of impairment of social dysfunction during the last 30 days. The scale covers four areas of social functioning, namely socially useful activities such as occupation and study, personal and other social relationships, self-sufficiency, and aggressive or otherwise disturbing behavior. The level of dysfunction in each area is rated on a 6-point Likert scale.

Statistical analysis

According to the MINI interview, three participants did not fully meet diagnostic criteria for AUD. For each case, we contacted their therapist and re-evaluated the results of the MINI interview together with them. For all three patients we could ensure that diagnostic criteria for AUD were, in fact, fulfilled. One participant had been abstinent for approximately 13 months prior to the interview, formally being considered as remitted. Since the patient was still in outpatient treatment for AUD and, at the time of the first contact with the study personnel, still fulfilled the criteria for AUD, they were included in the study. One patient could only partially conduct the interview; his missing data was imputed by median scores.

First, the alcohol and substance use patterns and craving of abstinent versus and consuming participants were compared by either unpaired *t*-tests for continuous data or Mann–Whitney-U-tests or χ^2 statistics for discrete data, where appropriate.

We used Kendall's Tau b to assess correlations between negative symptoms scores and RAP and craving scores, respectively.

We compared our study sample in terms of negative symptomatology with two other subsamples consisting of patients with schizophrenia and bipolar disorder from a study by Kirschner et al. This sample is described in detail elsewhere (84). To test whether the study sample differed from patients with either schizophrenia or bipolar disorder on negative symptoms of interest, we performed oneway analysis of variance with disorder group as dependent variable and age, duration of disease, BNSS MAP, BNSS DIM and BNSS total scores as independent variables.

Finally, multiple linear regression was used to test whether depressive symptoms (CDSS total score), negative symptoms (BNSS MAP and DIM factor subscores), and alcohol drinking during the last 30 days were associated with the extent of craving (OCDS score). The conditions of linear independence, normal distribution of the dependent variable and residuals, homoscedasticity, and absence of multicollinearity (i.e., variance inflation factors all < 1.96) were met. As a goodness-of-fit measure for the model we used the adjusted R^2 as it provides the percentage of variation explained by only the independent variables that actually affect the dependent variable.

All statistical analyses were conducted using SPSS Statistics Version 27. Given the exploratory nature of this pilot study we did not control for multiple comparisons and set the level of significance at $p < 0.05$ for all calculations.

Results

Demographics and sample characteristics

In total, 42 patients were included in the study and completed the clinical interviews. Detailed demographic characteristics of the sample are shown in **Table 1**. Over one third ($n = 16$) of the participants reached cut-off values for significant clinical depressive symptoms in the ADS-L and CDSS. Only eight participants had no psychiatric comorbidities, whereas almost half of all participants had more than one comorbid psychiatric disorder. Most patients ($n = 35$) had been formerly hospitalized more than once.

In detail, according to the MINI interview, the following comorbidities occurred within our sample: MDD: $n = 12$, dysthymia: $n = 10$, panic disorder: $n = 10$, agoraphobia: $n = 9$, social phobia = 7, generalized anxiety disorder: $n = 10$, obsessive-compulsive disorder (OCD): $n = 1$, posttraumatic stress disorder (PTSD): $n = 9$, bulimia nervosa: $n = 3$, antisocial personality disorder: $n = 5$. Consistent with the exclusion criteria, there were no patients with psychotic or bipolar disorder in our sample.

According to the MINI, more than one third ($n = 15$) of the patients fulfilled criteria for an additional substance use disorder, with cannabis use disorder being the most common ($n = 8$). sedative, hypontics and anxiolytic use disorder ($n = 4$), cocaine use disorder ($n = 2$), stimulant use disorder ($n = 1$), and opioid use disorder ($n = 1$) were also present.

Table 2 displays the current psychopharmacological medication of the study participants. There were only two participants in the sample who did not report any intake of psychopharmacological medication. Almost half of the study population ($n = 20$) had been prescribed antipsychotics; antidepressants ($n = 30$) and benzodiazepines ($n = 22$) had been prescribed to more than half of the participants. Stimulants were also prevalent in the sample ($n = 13$).

TABLE 2 Medication listed by substance class.

Characteristic	*N*	%
Antipsychotics	20	47.6
Opioids	4	9.5
Benzodiazepines	22	52.4
Antidepressants	30	71.4
Stimulants	13	30.9
Other	35	83.3
No medication	2	4.8

Antipsychotics: Low-potency antipsychotics predominantly have a sedative, not an antipsychotic effect. The category *Other* includes relapse prevention medication, analgesics, and medication for the treatment of somatic diseases.

Alcohol use

The pattern of alcohol use within the sample is shown in Table 3. Of 42 participants, 38 met diagnostic criteria for AUD within the past 12 months before inclusion in the study. Two participants had shown a harmful alcohol use within the past 30 days but did not meet the diagnostic criteria of current alcohol dependence. One had been abstinent for 13 months and was thus regarded as fully remitted (9). One participant did not answer questions concerning alcohol use.

Out of all participants, 10 had been abstinent from alcohol use for at least 30 days (30–400 days). Apart from the duration of abstinence, these participants did not differ significantly from the actively consuming group regarding their alcohol and substance use patterns and craving, respectively.

Group comparison with patients with schizophrenia and bipolar disorder

Using oneway ANOVA we compared our sample with two subsamples from another study population consisting of patients either with schizophrenia or with bipolar disorder. The three groups differed significantly in regards of age and duration of disease. With respect to the extent of negative symptoms, the ANOVA revealed no significant between-group differences for BNSS total scores as well as BNSS MAP and DIM scores (BNSS total: ($F(2, 91) = 1.55$, $p = 0.219$, BNSS MAP: $F(2, 91) = 0.26$, $p = 0.773$, BNSS DIM: $F(2, 91) = 2.66$, $p = 0.075$).

Negative symptoms and severity of alcohol use disorder

The BNSS total score was significantly correlated with the RAP score ($\tau_b = 0.228$, $p = 0.043$, 95% CI [0.022, 0.416]). On the level of negative symptoms factors, we found a significant correlation between the BNSS MAP subscore and the RAP total score ($\tau_b = 0.223$, $p = 0.049$, 95% CI [0.016, 0.411]). The DIM factor subscore of the BNSS, in contrast, did not significantly correlate with the RAP score ($\tau_b = 0.205$, $p = 0.076$, 95% CI [-0.002, 0.395]). For details see Table 4.

The SNS total score did not show a significant correlation with the RAP score ($\tau_b = 0.201$, $p = 0.076$, 95% CI [−0.007, 0.392]).

TEPS scores (total score, as well as subscores for anticipatory and consummatory anhedonia) and the CDSS total score were also not correlated with the RAP score (data not shown).

Negative symptoms and craving

Non-parametric correlations

The total score of the BNSS scale was positively correlated with the OCDS total score as a measure of craving ($\tau_b = 0.387$, $p < 0.001$, 95% CI [0.196, 0.550]). This was also the case for the MAP factor subscore of the BNSS ($\tau_b = 0.425$, $p < 0.001$, [0.239, 0.581]). However, the DIM factor subscore did not show a significant correlation with the OCDS total score ($\tau_b = 0.204$, $p = 0.069$, [−0.003, 0.395]). All data are provided in Table 4.

The SNS total score as a self-report measure for negative symptoms was significantly correlated with the OCDS total score ($\tau_b = 0.275$, $p = 0.013$, 95% CI [0.072, 0.456]). TEPS scores (subscores for consummatory and anticipatory anhedonia as well as the total score), in contrast, did not show a significant correlation with the OCDS score (data not shown).

Depressive symptoms as measured with the CDSS total score were significantly correlated with the OCDS total score ($\tau_b = 0.387$, $p < 0.001$, 95% CI [0.195, 0.550]).

Multiple regression analyses

The results obtained from the regression analysis are shown in Table 5. Multiple linear regression was used to test whether depressive symptoms. negative symptoms (MAP and DIM factor) and alcohol drinking during the last 30 days were associated with the extent of craving as measured by the OCDS. The overall regression model was significant [$F(4, 37) = 9.003$; < 0.001] and explained 44% of alcohol craving. with the BNSS MAP factor ($\beta = 0.452$; $t = 2.78$; $p = 0.008$) and number of drinking days in the last 30 days [($\beta = 0.233$; $t = 2.03$; $p = 0.049$)] being significant predictors of craving. The CDSS score and the BNSS DIM factor subscore were not significantly associated with the OCDS score.

Alcohol use pattern and negative symptoms

The duration of lifetime harmful alcohol consumption as assessed *via* TLFB did not correlate with the BNSS total score ($\tau_b = 0.040$, $p = 0.712$, 95% CI [−0.168,

TABLE 3 Alcohol use and dependence pattern divided by current consumption and abstinence.

	Abstinent (N = 10)				Consuming (N = 32)				
	M	N (%)	SD	Range	M	N (%)	SD	Range	P
Onset harmful use	26.80		13.05	13–51	24.63		11.26	12–57	ns
Duration harmful use	15.40		11.57	2–40	19.22		12.68	1–40	ns
Severity of addiction	9.80		2.25	6–13	9.42		1.84	6–12	ns
Amount of alcohol in last 7 days in grams/in a typical week	119.93		81.26	27–301	118.80		106.81	6–392	ns
Duration abstinence in days	162.70		118.34	30–400	6.14		7.85	0–30	*
Regular consumption of other substances		4 (40)				19 (59.4)			ns
Additional substance use disorder (MINI)		4 (40)				11 (34.4)			ns
Craving									
VAS currently	9.50		26.40	0–84	25.16		31.50	0–100	ns
VAS 7 days	15.00		24.97	0–84	55.19		30.28	0–100	**
OCDS	14.10		9.56	4–35	20.03		8.19	4–40	ns

*$p < 0.05$, **$p < 0.01$, ns = not significant. The alcohol use and dependence pattern were collected with the substance consumption schema and craving with a Visual Analogue Scale (VAS) and the Obsessive Compulsive Drinking Scale (OCDS). Percentages are indicated in parentheses. The MINI data is missing from one participant.

TABLE 4 Correlations between BNSS MAP, BNSS DIM, BNSS Total scores, and severity of AUD (RAP), craving (OCDS), and social functioning (PSP).

			BNSS			RAP	OCDS	PSP
			MAP	DIM	Total			
BNSS	MAP	Correlation Coefficient r	–					
		p (2-tailed)	.					
		95% CI			–			
	DIM	Correlation Coefficient r			,322**	–		
		p (2-tailed)			,004	–		
		95% CI			0.123, 0.496	–		
	Total	Correlation Coefficient r	,755**	,589**	–			
		p (2-tailed)	,000	,000				
		95% CI-	0.649, 0.832	0.435, 0.710	–			
RAP		Correlation Coefficient r	,223*	,205	,228*	–		
		p (2-tailed)	,049	,076	,043	–		
		95% CI	0.016, 0.411	-0.002, 0.395	0.022, 0.416	–		
OCDS		Correlation Coefficient r	,425**	,204	,387**	,226*	–	
		p (2-tailed)	,000	,069	,000	,047	–	
		95% CI	0.239, 0.581	-0.003, 0.395	0.196, 0.550	0.020, 0.414	–	
PSP		Correlation Coefficient r	,222*	,197	,233*	,557**	,226*	–
		p (2-tailed)	,048	,086	,038	,000	,046	.
		95% CI	0.016, 0.410	−0.011, 0.388	0.027, 0.420	0.396, 0.685	0.019, 0.413	–

*$p < 0.05$, **$p < 0.01$. CI = confidence interval. BNSS MAP, Brief Negative Symptoms Scale motivation and pleasure factor; BNSS DIM, Brief Negative Symptoms Scale, diminished expression factor; BNSS Total, Brief Negative Symptoms Total Score; RAP, Rapid Addiction Profile Score; OCDS, Obstructive Compulsive Drinking Scale score; PSP, Personal and Social Performance Scale score.

0.245]), the BNSS MAP score (τ_b = 0.162, p = 0.139, 95% CI [−0.047, 0.357]), or the BNSS DIM score (τ_b = −0.084, p = 0.450, 95% CI [−0.286, 0.125]). The amount of alcohol consumed during the last week was also not correlated with neither the BNSS total score (τ_b = 0.035, p = 0.745, 95% CI [−0.173, 0.241]), the BNSS MAP score (τ_b = 0.024, p = 0.828, 95% CI [the BNSS MAP score 0.184, 0.230]), nor the BNSS DIM score (τ_b = 0.080, p = 0.471, 95% CI [−0.129, 0.282]).

Social performance and negative symptoms

There was a significant correlation between the PSP total score and the BNSS total (τ_b = 0.233, p = 0.038, 95% CI [0.016,

TABLE 5 Multiple linear regression with OCDS total score as the dependent variable and CDSS, BNSS MAP, BNSS DIM, and drinking days last 30 days as independent variables (N = 42).

Variable	B	SE	β	t	p	95% CI	
						LL	UL
Constant	6.253	2.553		2.367	0.023	0.900	11.607
CDSS (total score)	0.317	0.230	0.197	1.307	0.199	−0.175	0.810
BNSS MAP (total score)	0.388	0.133	0.452	2.783	0.008	0.106	0.671
BNSS DIM (total score)	0.166	0.164	0.128	0.983	0.332	−0.176	0.508
Drinking days last 30 days	0.802	2.325	0.239	2.033	0.049	0.003	1.601

adj. R^2 = 0.438; F(4.37) = 9.003; $p < 0.001$. CI, confidence interval; LL, lower limit; UL, upper limit. CDSS, Calgary Depression Scale for Schizophrenia; BNSS MAP, Brief Negative Symptoms Scale. Motivation and pleasure factor; BNSS DIM, Brief Negative Symptoms Scale diminished expression factor.

0.410]), as well as the BNSS MAP score (τ_b = 0.226, p = 0.048, 95% CI [0.027, 0.420). The BNSS DIM score, in contrast, was not significantly correlated with the PSP total score (τ_b = 0.197, p = 0.086, 95% CI [−0.011, 0.388]). SNS, TEPS, and CDSS scores were not correlated with the PSP score (data not shown).

Discussion

To our knowledge, this pilot study is the first to apply the two-factor model of negative symptoms of schizophrenia to a sample of patients with AUD.

In comparison with two samples (84) of patients with either schizophrenia or bipolar disorder, our study sample of patients with AUD showed no significant difference in the extent of negative symptoms. This finding suggests that negative symptoms that have been established as a key element of psychotic disorders are also prominent in AUD. Furthermore, there was a positive correlation between the severity of AUD as measured with the therapist-rated RAP and both the total score and the MAP factor score of the BNSS. A possible explanation is that chronic elevated alcohol use leads to changes within neural circuits that are involved in motivation and reward similar to changes that occur in schizophrenia. Diminished expression, in contrast, was not correlated to the severity of AUD.

The BNSS total score as well as the MAP factor subscore showed a significant correlation with self-reported extent of alcohol craving. While other studies have already established a correlation between anhedonia and craving (51, 67), our findings suggest that a dysfunction in a somewhat broader motivational process may be a driving factor for craving. This finding was further supported by a multiple regression analysis comparing negative and depressive symptoms in their effect on the severity of AUD, which showed that 44% of the variation of the extent of craving within our population could be explained by the BNSS MAP score and the drinking days in the past 30 days. In contrast, the DIM factor subscore was not associated with the extent of craving.

These results support the hypothesis that during the course of AUD adaptations occur withing the neural pathways involved in motivation and reward. The fact that negative symptoms within the DIM domain were not correlated with craving is in line with this interpretation.

In our sample, there was no correlation between lifetime duration of harmful alcohol use as well as the total amount of alcohol consumed, and the extent of negative symptoms. This is probably due to the small sample size. However, factors other than substance use, e.g., comorbidity or psychosocial stressors, could theoretically be responsible for the development of negative symptoms in our participants.

The findings of this pilot study are exploratory in nature and have to be replicated in other samples. If reproduced, the association of negative symptoms with severity of AUD as well as the extent of alcohol craving within these patients may have therapeutic implications. In contrast to negative symptoms in schizophrenia which are often difficult to treat (85), there is growing evidence that motivational deficits in patients with AUD can be addressed therapeutically. In a study by Kirschner et al., for example, patients with cocaine use disorder successfully activated their reward system with mental imagery and real-time fMRI neurofeedback (86). In a pilot study, Pettoruso et al. successfully treated patients with cocaine use disorder with repetitive transcranial magnetic stimulation to improve anhedonia (87). Interestingly, the NMDA receptor antagonist ketamine which has shown remarkable preliminary results in the treatment of SUDs (88, 89), also seems to have significant anti-anhedonic effects (90, 91).

The present findings should be handled cautiously. Substantial study limitations include non-random sampling, a small sample size, the absence of a comparison group, and non-adjustments for multiple testing. Notably, the majority of patients within our sample had at least one psychiatric comorbidity limiting the internal validity of our study since it

cannot be ruled out that these comorbid disorders contribute to the extent of negative symptoms. However, our naturalistic sample increases the external validity since psychiatric comorbidities are the rule rather than the exception in AUD and other SUDs (92, 93). We examined the correlation of MDD and severity of AUD and craving, respectively as MDD is among the most common comorbid disorders of AUD (94) and shares anhedonia as a common feature with negative symptoms. Anxiety disorders and antisocial personality disorder were also frequent in our sample. To our knowledge, there are no studies examining the occurrence of negative symptoms in these disorders but of course our study cannot rule out a possible impact of these comorbidities on negative symptoms.

Posttraumatic stress disorder was present in nine patients. Adverse childhood events have been linked to AUD (95, 96) as well as positive and negative symptoms in schizophrenia (97). Future research should investigate the nature of a possible interrelation between PTSD and negative symptoms in AUD. We further used a cross-sectional approach and did not assess important parameters, such as an objective measure of alcohol intake, a valid measure for the severity of AUD. Furthermore, the RAP that we used to assess overall severity of AUD, which is a reliable clinical tool, has not yet been validated in other studies.

Taken together, however, our findings provide first evidence that negative symptoms are prevalent in AUD to an extent that does not differ significantly from other major psychiatric disorders, are correlated with disease severity and craving, and therefore might constitute a novel and promising therapeutic target that should be addressed in future clinical trials to improvement treatment outcomes for patients with AUD.

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 Cantonal Ethics Committee, Zurich, Switzerland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MB, KD, and MH designed the study with assistance from MK and SK. GF and JH performed all the clinical interviews and collected all therapist-rated measurements. MK instructed GF and JH in the assessment of all negative symptom scales. GF, JH, KD, and MB analyzed the data. MB wrote the manuscript with input from all authors. All authors contributed to the article and approved the submitted version.

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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A specific cognitive behavioral group therapy program for stimulant use disorder

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Introduction: Stimulant use is an important health issue. In the US in 2018, 2.8% of males and 1.5% of females older than 18 had used cocaine in the preceding 12 months.

Objective: To intervene in a specific targeted group of Stimulant Use Disorder (SUD) patients according to CBT and relapse prevention theories, and to determine the program's feasibility and attendance.

Method: Stimulant Use Disorder patients in addiction care were evaluated for addictive, psychological and psychiatric dimensions at baseline and conclusion in a 9-session CBT group program with several themes: define SUD, enhance motivation, involve close companions, cope with craving, decline a proposal, solve problems, invite expert patients, invest time and money, and review content.

Results: In total, 41 patients attended at least one session. They were mainly poly dependent, primarily cocaine users. Sixty percent of the population also suffered from another psychiatric comorbidity. Median attendance for participants was 7/9 sessions.

Conclusion: A specific targeted CBT group for stimulant dependent highly comorbid patients is feasible. These findings suggest that peers should be included in addiction care services.

KEYWORDS

group therapy, substance use disorders, cocaine (PubChem CID: 11302220), Cognitive Behavioral Therapy (CBT), craving

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Introduction

Prevalence

Stimulant use is an important health issue. In the US in 2018, 2.8% of males and 1.5% of females older than 18 had used cocaine in the preceding 12 months (1), a number close to that in Europe in 2019, where 2.1% of 15 to 34 year olds had taken cocaine in the past 12 months, 1.4% amphetamines, and 1.9% MDMA (3,4-Methylenedioxymethamphetamine). In France these numbers are even higher (3.2, 0.6, and 1.3%, respectively) (2). The use of New Synthetic drugs, including cathinones and the non-stimulant synthetic cannabinoids is estimated at 1.1% among this same population in Europe. For the methamphetamine, some countries include it in their amphetamine use data and the prevalence rate seems to be highly variable, between 330 and 34,600 users at risk per country.

Stimulants use, including cocaine, has many consequences, including somatic (infarctus, pulmonary insufficiency, stroke. . .) (3, 4), psychiatric (a higher incidence of anxiety disorders or induced psychotic symptoms) (5, 6), and social consequences. Moreover, in the United States from 2010 to 2014, on average 7,500 of the 40,000 overdoses per year involved stimulants (cocaine or methamphetamine), and overdoses per year with these substances are rising (7).

Specificities of stimulant users

Stimulant users attending care programs represent a specific population in many ways. Indeed, they are at high risk of experiencing delusional thinking (30% of cocaine-dependent patients) and unusual social or sexual behavior (65%) (5). They show a very strong association with childhood trauma. A previous study found that 62% of cocaine users had experienced such trauma (8). Furthermore, cocaine users are largely poly users. In another study they presented a median of three lifetime DSM IV dependence to other substances than cocaine (9). These substances were mostly "downers," substances sharing sedative properties (alcohol, benzodiazepine, and cannabis), so patients are likely to use them to prevent coming-off effects.

In France, among stimulant users, cocaine users who entered treatment centers are mostly men (80%) and on average started cocaine at 24 years old and entered the center at 33 years old, meaning that there is a great delay between first use and treatment access (10). The management of stimulant users is characterized by several barriers to treatment. In substance abuse clinics, 34% quit the process within two months, and cocaine-related issues increased the risk of early drop-out (11). Of methamphetamine users, only 23% of outpatients remained in treatment after 180 days (12).

Moreover, significant neurocognitive impairment has been shown among cocaine users (13). A meta-analysis suggests that impulsivity is a core process underlying addictive disorders (14). A study comparing cocaine users to healthy controls found that cocaine users have elevated scores on trait impulsivity and have significantly poorer performance on inhibition and perseveration (15). Furthermore, dependent cocaine users display broad cognitive impairments in the domains of attention, working memory, declarative memory, and executive functions compared to recreational users or non-cocaine users (16).

Treatment

Because there are no validated pharmacotherapies for stimulant treatment, psychotherapy seems to be an important part of the treatment. Cochrane Library published a meta-analysis in 2016 of 52 controlled randomized trials of psychotherapies for stimulant treatments, finding that all individual interventions diminished drop-out rates and enhanced abstinence (17). Another meta-analysis in 2018 of studies of cocaine and amphetamine users found that the combination of two different psychosocial interventions, contingency management and community reinforcement, was the most efficacious and accepted treatment in the short and long term (18). More recently, a systematic review published in 2020 states that no pharmaceutical intervention has proven its efficacy and the most promising psychological intervention was Contingency Management (CM). This therapy seems to have a short-term efficacy on abstinence. Moreover, the combination of CM and Cognitive Behavioral Therapy might be the most efficient therapy with a higher rate of abstinence, a lower drop out and probably more long-term effect. About CBT alone, the authors conclude that more research is needed to ensure its efficacy, particularly on abstinence (19).

The French High Health Authority recommends individual psychotherapy, such as Cognitive Behavioral Therapy (CBT), for cocaine dependence and states that groups could provide an interesting complement (20). They suggest a number of themes that could be discussed: Managing craving, enhancing motivation, gaining competences to resist solicitations, recognizing high-risk situations, generalizing strategies to face the desires to consume, and solving urgent problems that could pose the risk of using cocaine. Furthermore, Marlatt and Donovan suggest that Relapse Prevention for stimulant use should include an initial evaluation with common objectives, then a large part of the therapy should focus on cravings (trigger identification, exposition, refusal to use, alternative strategies, etc.) (21). Stimulant use can cause neuropsychological impairment that must be taken into account before engaging in any therapy, and it is preferable to postpone the relapse

prevention program after a neurocognitive training to enhance the efficacy (22).

Because of the cost of the individual setting and the contribution of peer groups, there have been several studies of group therapies for stimulant users. The Matrix Program combines individual and group sessions (relapse prevention, 12-step, family, and social support groups) (23). Furthermore, Tzilos et al. developed a contingency model for cocaine users in methadone-maintained treatment. Among them, 26% never came to any session and 62% were non-completers (completers were defined as patients who came to at least six consecutive sessions with cocaine-negative urine samples) (24). A Spanish team developed a combined CBT and motivational open group 12-session program for cocaine users that demonstrated a very high retention rate (84%) (25). A study comparing CBT and Mindfulness Treatment (MT) open groups among drug users (alcohol and/or cocaine) showed high drop-out and similar drug reduction in both groups (26). In this study, the CBT program was implemented according to the National Institute for Drug Abuse guidelines (27). They suggest several topics to work with the patient: Coping with craving, shoring up motivation and commitment to stop, refusal skills/assertiveness, seemingly irrelevant decisions, coping plans, problem solving, case management, and HIV or other infectious risk reduction.

Several studies of cocaine treatment include avoidance and reinforcement components, but a large study illustrated the ineffectiveness of punitive approaches and highlighted the potential of improving goal-directed behavior and employing more desirable habits to replace drug-taking habits, such as CBT approaches (28). The third wave of CBT approaches, specifically Mindfulness Based Interventions, seems to have a significant effect on craving and substance misuse, so this approach could constitute a useful therapy for addiction treatment (29).

Therefore, the aim of this study was to intervene in a specific, targeted group for stimulant dependent patients. Few sessions were designed to take into consideration the impulsivity and lack of persistence of these patients in order to enhance attendance. The conceptual framework was CBT and relapse prevention theories. The secondary objective was to observe the feasibility, acceptability, and attendance in this group.

Materials and methods

Participants

Participants were recruited from the clinical outpatient department of a university hospital in Paris (France). Potential participants were identified by their treating psychiatrist or psychologist. The inclusion criteria were: (1) regularly followed French-speaking patients, (2) met diagnostic criteria of Substance Use Disorder (SUD) according to the Diagnostic and Statistical Manual for Mental Disorder 5 (30) for any stimulants (cocaine, crack, amphetamines, methamphetamine, cathinones), (3) wanting to stop or diminish their consumption, and (4) without acute psychiatric symptoms preventing group participation such as current delusion, hallucinations, mood instability, or suicidal ideation. No psychiatric diagnosis was excluded. All participants joined the same therapy program as an add-on to their usual outpatient psychiatric and addiction medicine care.

Ethics

The study was conducted according to the Declaration of Helsinki and the French legislation on biomedical research in human subjects (Loi Jardé 2014), as well as the ethical guidelines of our hospital for the analysis of data already collected during routine care (Authorization 2017–013 given on 19 January 2017 by the CNIL, the Commission Nationale Informatique et Liberté, or French National Board for Information Systems and Freedom). Verbal consent to participation and research application of the data was obtained from all participants after information. Furthermore, specific information and consent was obtained for relatives' participation.

Assessment at entry

Eligible participants were invited to an initial visit to discuss participation and receive information about the group therapy program, rules, and assessments in the month before the session started.

Clinical evaluation

Socio-demographic data was collected in a semi-directed interview with the therapist, as well as substance use histories (substance use disorders, age at onset, and routes of administration). Psychiatric diagnoses and actual psychotropic treatment were recorded from the medical record. Attendance was recorded as the number of sessions attended by each individual and participant subjective feed-back was recorded during the last session (no. 9).

Hospital anxiety and depression

Actual anxiety and depression were assessed using the HAD (Hospital Anxiety and Depression) screening questionnaire, a 14-item self-rated questionnaire that evaluates anxiety and depression during the past week (31). A Canadian study showed that this measure seems to have a good level of reliability with Cronbach alpha around 0.8 and confirm the two factors measure with anxiety and depression subscales. Their results were similar among the general population and multimorbidity patients (32).

Timeline followback

Stimulant frequency and intensity of use were evaluated with the TLFB (TimeLine Followback) questionnaire. This tool is a calendar (initially developed for alcohol consumption) in which patients note when they use a drug and how much (33). The tool has proven its reliability using test-retest comparison for several substances. Also, the TLFB has demonstrated its validity, being highly correlated with the Addiction Severity Index and discrimination with high correlations with urine sample analysis (34).

Brief situational confidence questionnaire

Self-confidence was recorded with the BSCQ (Brief Situational Confidence Questionnaire) questionnaire, a state-dependent measure that assesses self-confidence to resist the urge to use a drug in several situations with 8 items in a Visual Analogic Scale (35). A study among incarcerated youth highlights a good test-rest stability (Pearson's r around 0.60) and internal consistency (Cronbach's alpha around 0.85) (36).

Obsessive compulsive craving scale

Craving was assessed using the OCCS questionnaire (Obsessive Compulsive Craving Scale), which is a 14-item questionnaire with a total score and two subscales: obsession and compulsion during the last 2 weeks (37). This same study shows a Cronbach's alpha of 0.93. It also highlights a high correlation with the Visual Analog Scale (Pearson's $r = 0.641$).

University of rhode island change assessment

The motivation to change was evaluated with the URICA (University of Rhode Island Change Assessment), a 32-item self-rated questionnaire to evaluate change motivation on four subscales (pre-contemplation, contemplation, action, and maintenance), with a total score calculated by adding the scores for contemplation, action, and maintenance and subtracting the pre-contemplation score (38). Each subscale has good internal consistency with Cronbach's alpha ranging from 0.81 to 0.88 (39).

Design of the therapeutic intervention

This closed group consisted of nine sessions with two therapists, each of 1.5 h duration. The authors did design this group intervention according to classical Relapse Prevention themes (21, 40, 41). The synthetic themes of each session are presented in **Table 1**. Sessions included several themes such as: a common definition of TUS according to DSM 5 (30), introduction to motivational interviewing and Prochaska and Di Clemente's theory (42); introduction to assertiveness principle (43), solving problem strategies (44) and relaxation (19, 45).

Statistical analysis

Variables are described using means (Standard Deviation) and percentages. When a patient did not answer all questionnaires, only available data was analyzed. This was also the case for drop outs. The distribution normality was checked. Comparison between pre and post intervention were tested using Khi^2 and Repeated Measure Anova or Wilcoxon as appropriate, with a $p < 0.05$ threshold. The analysis were done using JASP 0.8.6.0 software.

Results

Population description

The 41 patients who came to at least one session were recruited between June 2017 and November 2019. They were on average 43 years old; 73% were men, 26% did not have their own housing, 58% had a job, and 58% were single. Regarding stimulant use, patients preferentially used cocaine (65%) over other stimulants and preferred snorting cocaine (68% vs. injection or smoking). The mean age at onset of stimulant use was 28 years old (± 10 years). They had an average of 1.2 grams or 3 rocks per day of stimulant use.

Concerning other substances, 61% were currently dependent on tobacco, 62% on alcohol, 12% on cannabis, and 2% on opiates (among whom all were on agonist maintenance treatment).

Regarding their current psychiatric component (according to their medical records), 40% did not have any psychiatric comorbidity, 30% had mood disorder, 12.5% personality disorder, 10% anxiety disorder, and 2% schizophrenia. Twenty nine percent of the patients had no prescribed psychotropic treatment, 33% had antidepressants, 37% antipsychotics [including aripiprazole prescribed as anti-craving treatment (46)], 28% benzodiazepines, and 28% mood-stabilizer treatment.

Results and time course of the scores on assessment tools

Detailed results are presented in **Table 2**. The TLFB questionnaire showed that in the month before the group started, patients had a mean of 7 days of stimulant use. The median of the frequency of the number of days of abstinence was 76%. The OCCS craving mean total score was 18.9 (±7.4) in a range from 0 to 56, where a higher score indicates higher craving. The subscales were largely equivalent, with a mean obsessive score of 8.5 and a mean compulsive score of 10.4. The mean URICA score was 88 (±11.4) on a possible range of −16–112, where higher scores indicate greater motivation

TABLE 1 Sessions and themes.

Session	Theme	Content
1	**Define substance use disorder:** • Patient's criteria • DSM 5	The patients fill the questionnaires, then the therapists remind them the rules of the group (listening, non-judgment attitude and confidentiality, attendance, punctuality, the need to come sober) and give patients a booklet containing session titles and empty spaces to be completed during the sessions. The aim of this session is to create a link among patients and to define Substance Use Disorder (SUD) according to the Diagnostical and Statistical Manual 5 definition (DSM 5). Patients perform a photolanguage exercise. They have to pick an image that defines their stimulant dependence and explain why. From this material, patients define their own SUD criteria, eventually completed by the therapist. Finally, harm reduction strategies are proposed.
2	**Enhance motivation:** • Present stages of change • Decisional balance	This session focuses on change, following Prochaska and Di Clemente's theory and Miller and Rollnick's model of motivational interviewing. Therapists first present the model of change with its different stages: pre-contemplation, contemplation, preparation, action, maintenance, and relapse. Patients and therapists then perform a decisional balance of four cases: the pros and cons of existing behavior and behavior change (the change considered can be abstinence or use reduction).
3	**Relatives** • Inform about addiction • Work on attitudes	Each patient can invite a relative (friend, family, or partner). The purposes are both to answer the relative's questions about addiction and to aid the relative in helping the patient. The therapists give general information without disclosing personal and confidential information to the patient's relative. The importance of confidentiality is stressed to patients and relatives.
4	**Coping with craving** • Triggers list • Craving definition • How to cope with craving	This session starts with a brainstorming of what could lead to craving (situation, paraphernalia, propositions, etc.). The therapists then illustrates the craving curve, showing craving rising after triggers and cues; craving reduction after use; and even without drug use, showing the interest of surfing on the craving wave. The last part of this session is dedicated to finding solutions to cope with craving without using drugs.
5	**Decline a proposal** • Define assertiveness • How to refuse • Role playing	The aim of this session is to learn how to decline to use/buy drugs through the assertiveness principle. Therapists start by defining assertiveness as standing up for your personal rights by expressing thoughts, feelings, and beliefs in direct, honest, and appropriate ways. Patients are trained to refuse, without aggressiveness and while taking body language into account, according to the following steps: Respond with a clear and firm "no"; Explain why you say no shortly and without justifying yourself; Broken record: Don't add further explanations; Terminate the conversation. The final part of this session is role-playing where two patients act out a scene where one is a tempter and the other a user who has to refuse. The other patients are observers who note verbal and non-verbal assertive communication. A debriefing review what was well done and what needed to be improved. All patients perform both roles (tempter and tempted).
6	**Solving problems** • Choose a patient's problem • Experiment the solving problem strategy	This session focuses on solving-problem techniques starting with a situation proposed by one participant. The steps are as follows: Define the problem, list all the possible solutions, for each solution list the pros and cons, pick the solution with the most pros and the fewest cons, evaluate the necessary means, note if those means are available, and if so, determine concretely how to implement the solution. The aim is not only to help one patient, but also to explain the technique to all patients.
7	**Expert patient (explain his drug use and care trajectory)**	A former patient (expert patient) who had completed the program in 2015 came to explain his addiction care path to other patients. He explained what steps he went through and what helped him at each step. Patients could intervene at any time to comment or ask questions.
8	**Invest time and money without drug** • In a short/middle/long term perspective • Develop planning strategies	In this session patients imagine what would be their life if that they had stopped using drugs. More time and more money will be available, both of which are triggers that could lead to craving. The therapists thus encourage patients to develop plans to invest their time and money in drug-free behaviors. Furthermore, the therapists suggest that those plans should be short, mid, and long-term without drugs. For the short term, it could be planning of what to do in the next few weeks.
9	**Content review** • Open criticize group content • Jacobson relaxation	The patients fill all the initial questionnaires again. A complete feedback of the group is collected. Patients are invited to criticize the organization and content of the sessions. Jacobson relaxation is then performed and patients can record it on their smartphones or receive it by e-mail.

to change. The score can also be observed using stages. In this configuration, 25 patients had no equality between two stages and can be interpreted. We observe among those 25 patients that a half (52%) were in contemplation, 32% in action and 16% in maintenance; none was in pre-contemplation. The HAD anxiety mean score was 11.9 (±4.2) and the depression mean score was 7.9 (±4.7). Both scores highlight the presence of anxiety and depression symptoms (47). Furthermore, almost half of the population (N = 17), experiment depressive symptoms above the recommended screening cut off. Regarding anxiety screening, 90% of the participants experience symptoms above the cut off. The BSCQ self-confidence median was 350, the

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TABLE 2 Main assessment tools results.

	Pre-test $N = 41$			Post-test $N = 17$			Statistical pre-post tests
	Mean (SD)	Median	Frequency	Mean (SD)	Median	Frequency	Repeated measure ANOVA
TLFB (percentage of abstinence days in the previous month)	75.8 (27.5)	87.1		81.8 (23.2)	93.3		$p = 0.268$
OCCS total	18.9 (7.4)	18		16.5 (8.2)	17		$P = 0.169$
OCCS obsession	8.5 (3.9)	8		8.1 (3.9)	7		$P = 0.858$
OCCS compulsion	10.4 (4.3)	10		8.4 (4.8)	9		$P = 0.083$
URICA score	87.7 (11.4)	88		89.7 (10.4)	92		$P = 0.870$
URICA stages			0% pre- contemplation 52% contemplation 32% action 16% maintenance			0% pre- contemplation 54% contemplation 27% action 18% maintenance	
HAD depression	7.9 (4.7)	8	53.1% > cut off	6.6 (4.1)	6	28% > cut off	$P = 0.556$
HAD anxiety	11.9 (4.2)	11	91% > cut off	10.6 (3.5)	11	85% > cut off	$P = 0.049$
BSCQ total	361.9 (144.1)	350		444.7 (165.1)	496		$P = 0.835$
BSCQ mean	45.2 (18.0)	43.7		55.6 (20.6)	62		$P = 0.833$

SD, standard deviation; TLFB, timeline followback; OCCS, obsessive compulsive craving scale; URICA, university of rhodes island change assessment; HAD, hospital anxiety depression; BSCQ, brief self confidence questionnaire.

mean total score was 362 (±144) and the average score was 45.2 (±18.0), meaning that in the situations listed, patients felt that they were at a 45% risk of using the stimulant.

Among completers ($N = 17$), the percentage of abstinence days prior to the inclusion was 85.3% (measured with the TLFB) with no statistical diminution between baseline and the end of the intervention. There was no significant change either for the following variables: OCCS total score (mean 18.82 ± 7.6), obsession score (mean 8.2 ± 3.6), compulsion score (mean 10.4 ± 4.5); the BSCQ total score (mean 427.1 ± 115.5) or mean score (mean 53.4 ± 14.4); the HAD depression score (mean 7.1 ± 4.2) or the Anxiety score (12.1 ± 4.5), see Table 3. Among patients attending the last session, they did not all answer all questionnaires proposed. Furthermore, some tools were added after the beginning of the intervention, so were not proposed for the first patients.

Number of sessions and attendance, patients' views of the group session efficacy

The average number of sessions attended by patients was 5.7 (±2.8) out of 9 sessions. The median was 7 and the mode was 8 sessions (see Figure 1). Figure 1 also highlight that 6 patients only attend one session and 5 went for all sessions. The TLFB did not significantly change between the beginning and the end of the intervention, the mean rate of abstinence days was 76% at the beginning and 82% at the end (see Table 2). Regarding the median, it was 87% at the beginning and at the end 60% of the population had scores higher than the initial median. Among the 41 patients who came to at least one session, 5 came to all sessions and 4/15 were abstinent at the end of the group, that is, 26% (among 15 patients) or 9% (among 41 patients). Among the 16 patients who attended the last session, on the URICA scale, 11 subjects described a specific stage. A half (54%) were in contemplation, 27% in action and 18% in maintenance. Those scores are very similar to those at the beginning of the intervention. About the HAD, among the 14 patients who completed the evaluation at the end of the group, 28% experience depressive symptoms above the cut off and 79% for anxiety. Those frequencies are lower than at the beginning of the intervention. Among pre-post evaluated patients ($N = 13$), a Khi^2 was performed and depression rates above the cut-off significantly decrease ($p = 0.026$), this result is no longer significant for anxiety ($p = 0.140$).

Concerning self-efficacy, at the end of the intervention, 69% of the patients had a score above the median of the beginning of the group, what could suggest that they improve their self-efficacy feeling during the intervention, even if the attrition rate was high.

On the craving scale, 59% of participants diminish their total score on the OCCS between the beginning and the end of the intervention. This rate was lower on the obsession scale (41%) and higher on the compulsion scale (65%).

Participants' feedback was positive, as per the comments of patients attending the last session. For example, verbatim included that some patients learnt theoretical elements and appreciate to be with peers. On the other hand, patients

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TABLE 3 Completers evaluation.

	Pre-test $N = 17$			Post-test $N = 17$		
	Mean (SD)	Median	Frequency	Mean (SD)	Median	Frequency
TLFB (percentage of abstinence days in the previous month)	85.3 (17.1)	93.4		81.8 (23.2)	93.3	
OCCS total	18.8 (7.6)	19		16.5 (8.2)	17	
OCCS obsession	8.2 (3.6)	8		8.1 (3.9)	7	
OCCS compulsion	10.4 (4.5)	10		8.4 (4.8)	9	
URICA score	89.3 (12.9)	93		89.7 (10.4)	92	
URICA stages			0% pre-contemplation 60% contemplation 10% action 30% maintenance			0% pre-contemplation 54% contemplation 27% action 18% maintenance
HAD depression	7.1 (4.2)	9	53.8% > cut-off	6.6 (4.1)	6	28% > cut-off
HAD anxiety	12.1 (4.5)	12	84.6% > cut-off	10.6 (3.5)	11	85% > cut-off
BSCQ total	427.1 (115.5)	406		444.7 (165.1)	496	
BSCQ mean	53.4 (14.4)	50.6		55.6 (20.6)	62	

SD, standard deviation; TLFB, timeline follow back; OCCS, obsessive compulsive craving scale; URICA, university of rhodes island change assessment; HAD, hospital anxiety depression; BSCQ, brief self-confidence questionnaire.

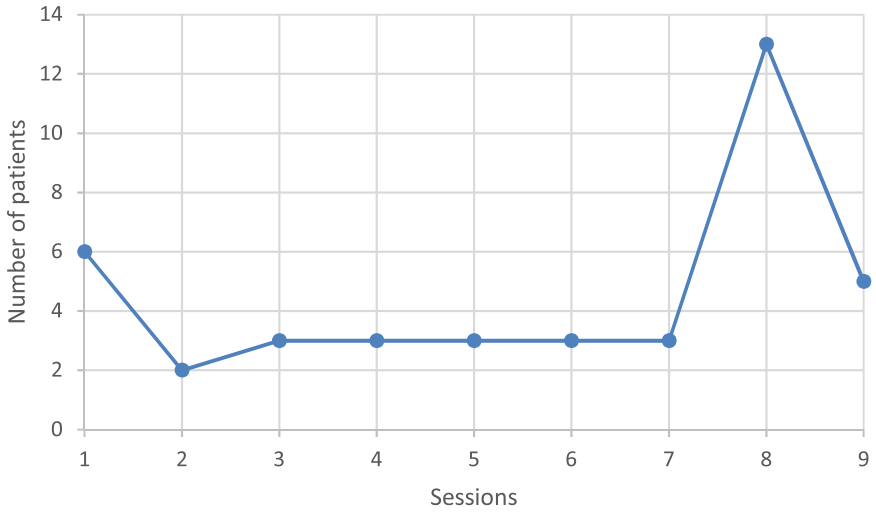

FIGURE 1
Attendance (number of sessions attended for each patient).

often told us that sessions could raise stimulant craving by talking about drugs.

Discussion

We designed a specific relapse prevention CBT group for outpatients with stimulant use disorder to address their specific need (poly dependence, induced delusions, alteration in social and sexual behavior, neurocognitive impairment, and childhood trauma).

Principal results

It is noteworthy that patients who attended the group sessions had 76% abstinent days in the month before the first session, raising the question of whether patients who came to the group were already highly motivated or had already initiated a change, such that only "*almost cured*" patients would attend this highly demanding type of care.

The observed OCCS total score was correlated with the frequency and intensity of use, and as patients had numerous

abstinent days, their scores tended to be intermediate between high and low craving (5).

The URICA score is high (mean = 88), indicating that the patients who could attend the sessions had a high motivation to change (48).

Attendance could be interpreted in different ways. Attendance could be seen as quite high, with a mode of 8 out of 9 sessions. Looked at another way, we also note that only 12% of patients went to all sessions. Furthermore, compared to previous studies, the attendance was good. One study (24) reported that 26% of patients never came to any session, whereas for ours the rate was 9.7%, but they had 62% non-completers (completers were defined as patients who came to at least 6 consecutive sessions with cocaine-negative urine samples), whereas in this study 58% came to at least 6 sessions. Another study (a CBT and motivational open group program of 12 sessions) among 19 patients, reported a high retention rate (84%), defined as attending 11/12 sessions (25). In comparison, in our study the retention rate was 44%, defined as attending eight to nine sessions, among patients who came to at least one session.

We did not observe a significant improvement in cocaine use or questionnaires' scores, but patients already had low scores at the beginning of the program. However, 4 of the 15 patients were abstinent at the end of the program.

Limitations

However, this study has some limitations. This study is an open study with no other group (control or other intervention). We thus might lack the power to demonstrate significant differences or patient improvement. Some of this lack of power could be due to the use of self-rated questionnaires only.

This group is hard to organize, in part because practitioners in our clinic did not easily refer patients to group therapies, and in part because it is difficult to constitute a homogenous group. However, patients attending the last session (who were asked to comment on the group) gave positive feedback about the help provided by the group, the organization, and session content.

In the future, we would like to raise the effectiveness of the program, explore the differences between the different stimulants, and change the tools to gain in sensibility.

Strengths

There are several strengths of this study. A specific intervention was designed to respond to the specific needs of stimulant user patients in a prospective study with pre-post evaluations. The study was conducted among patients affected by a disorders associated with poor compliance, and a good feasibility and acceptability were demonstrated. Moreover, this article partially responds to a previous article with a real life application of a group therapy in an out-patient treatment setting (49).

Perspectives

To improve this study, it would be interesting to increase inclusions to demonstrate patient improvement. An *a priori* test ($\alpha = 0.05$) for the difference between two means with matched pairs using the OCCS total score (one-tailed) suggests that the number needed to ensure sufficient statistical power is 67 patients, to whom both pre and post-evaluations would be applied. In order to confirm the efficacy, a comparison to another intervention, such as a computer-delivered program (50), is warranted.

Clinically, the content of the sessions could be enriched with mindfulness components and integrating psychoeducation on harm reduction on sexual behavior (51, 52).

This group intervention is feasible for patients suffering from stimulant use disorder and should be generalized in all care settings because the number of those patients is increasing in all care services without efficient pharmaceutical response.

Conclusion

This study presents a specific targeted CBT group program for severe poly dependent patients suffering from stimulant use disorder. Indeed, few interventions exist for this specific population. This group program proved feasible, even if most patients had difficulties attending all sessions.

Patients' recruitment in this study should go on to verify the efficacy of this therapeutic intervention. Furthermore, it would be interesting to add a follow up session, as well as to keep in contact with patients and to assess them again after the intervention.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

EK and MF designed the group program. EK, KP, and NT included the participants and performed the intervention. LR and FV designed the research protocol. All authors contributed to manuscript revision, read, and approved the submitted version.

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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Association of prescribed oral stimulants on cocaine use among patients enrolled in opioid agonist treatment: A retrospective longitudinal cohort study

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Objectives: The objective of this study was to measure the association of prescribed oral stimulants with the consumption of cocaine among a population of patients receiving Opioid Agonist Therapy (OAT).

Methods: The study was a retrospective clinical cohort study using the medical records of all patients receiving OAT who attended treatment clinics within the Canadian Addiction Treatment Centers (CATC) in Ontario from April 2014 to February 2021. Linear mixed-effects models were fit for the exposure of prescribed oral stimulants, and the outcome of a positive urinalysis drug screen for cocaine. Covariates for age, sex, and a random effect for patients were fitted to account for differences between and within patient observations over time.

Results: Among patients receiving OAT therapy n = 314 patients were prescribed oral stimulants and n = 11,879 patients were not prescribed oral stimulants among Ontario CATC clinics (n = 92, n = 145 physicians), the mean age at enrollment for patients receiving oral stimulants was 37.0, SD = 8.8, with 43.6% female patients and for patients not receiving oral stimulants mean age was 36.6, SD = 10.7, with 39.6% female patients. Linear mixed effects models showed no difference in cocaine-positive urine tests over time for fixed effects B = 0.001, however, when considering the Interclass correlation coefficient (ICC) between the fixed effects, we found that time since the prescription of an oral stimulant was associated with a decrease of ICC = −0.14 in cocaine positive urine tests. Increasing age at prescription ICC = −0.92, and being male ICC = −0.23 were associated with decreasing cocaine-positive urine.

Conclusion: The use of oral stimulant prescriptions to treat cocaine use had no clinically significant benefit in a real-world setting. Patients who

receive prescriptions for oral stimulants consume more cocaine before and after treatment compared to patients without an oral stimulant prescription. We also observed that cocaine use was reduced with increased time since treatment initiation.

KEYWORDS

retrospective longitudinal study, opioid agonist treatment (OAT), observational study, oral stimulation, cocaine use disorder

Introduction

Opioid use disorder continues to be a significant challenge in Ontario and worldwide (1, 2). According to the Public Health Agency of Canada report, the crude rate of total apparent opioid toxicity death in Ontario has increased over the years (3). There were 6.2 (per 100,000 population) opioid toxicity deaths in 2016 whereas the number increased to 16.4 (per 100,000 population) in 2020 (4). A large number of opioid-related toxicity death occur due to polysubstance use by individuals such as the use of cocaine and fentanyl (3).

Opioid Agonist Therapy (OAT) is currently the gold standard for patients with opioid use disorder (5, 6). In OAT, opioid withdrawal is managed by taking medications such as methadone or buprenorphine/naloxone. Although clinical guidelines recommend the use of OAT, data among specific sub-groups of patients receiving OAT is often absent or difficult to measure despite clinical interest because of differential health insurance coverage, and challenges in longitudinal follow-up of this patient population. These subgroups are of clinical interest because OAT could have variable effectiveness profiles in sub-populations, for example, those receiving oral stimulant medications and/or consuming cocaine (4, 7).

Cocaine is a stimulant that inhibits dopamine reuptake in the brain and long-term cocaine use is associated with declined cognitive functioning (8). In 2019, cocaine was the most commonly used illegal drug among Canadians, which accounted for approximately half of illegal drug use (9). Patients using cocaine while in OAT are especially concerning because 30–50% of OAT enrollees self-report cocaine use (10, 11). A previous study conducted by our research group showed that individuals in OAT who use cocaine have a lower retention rate in the treatment and early treatment discontinuation (4, 7). Additionally, a previous study in the United States has identified that OAT patients who regularly use cocaine are at increased risk of overdose (12). Therefore, interventions that reduce the consumption of cocaine among OAT patients could also improve treatment efficacy, outcomes, and persistence on OAT.

There is no pharmacological treatment available for cocaine use disorder (13). Recently, the use of oral stimulants for cocaine use disorder has gained some traction due to a small number of clinical trials conducted (14, 15). Among oral stimulants that have been considered promising to treat cocaine use disorder, bupropion and dextroamphetamine are considered to be effective for achieving sustained cocaine abstinence, according to a Cochrane Collaboration review of psychostimulant drugs (16). Because of the interaction between substance use, prescription of oral stimulants, and OAT, it is difficult to separate the association of these factors when they may exert complex or interlocking effects. Therefore, the use of a longitudinal clinical cohort with repeated measurements over time of both urinalysis testing and medication dispensation (OAT and oral stimulants) is needed to support limited trial evidence with observational data from a real-world clinical setting. Since the data collected was from patients with identical health insurance coverage, the confounder of multiple insurers was removed which could explain these complex relationships to investigate solutions that can help with reducing the frequency of cocaine use among OAT patients and improve patient persistence. The objective of this study was to measure the association of prescription oral stimulant medications on cocaine consumption among a population of patients receiving opioid agonist treatment.

Materials and methods

Study design and setting

The study was a longitudinal clinical cohort study with repeated measurements using the medical records of all patients receiving oral stimulants and already enrolled in OAT at The Canadian Addiction Treatment Centers (CATC) in Ontario from April 2014 to February 2021. In Ontario, the inclusion Manual version V (17). Ontario has a single-payer healthcare system, whereby all residents have identical health care coverage under the Ontario Health Insurance Plan (OHIP) with access to OAT. The CATC is the largest network of addiction medicine clinics in Canada (approximately 70 clinics across Ontario). CATC provides comprehensive care for patients who have substance use disorder which includes pharmacological therapy, primary care, harm reduction, and counseling. Standardized practices, policies, and operating procedures

within the clinic network, limit the likelihood of treatment variability between sites.

Participants and data sources

Enrollment criteria for the CATC were a Opioid Use Disorder requiring treatment with an OAT (including methadone and buprenorphine/naloxone), and patient age > = 18 years of age. No minimum follow-up date was enforced for this study, but patients must have at least one valid urinalysis test.

Participating CATC clinics were in Ontario with physicians and patients consenting to share data for research use. Data were collected using the EZMethPro electronic medical record system (18) with data available for each visit from the first visit until the end of follow-up or up to a maximum follow-up date of February 28, 2021. Urinalysis testing for opioids and controlled substances were conducted for each patient at ratio randomization intervals generated automatically by the electronic medical record system across the patient population. Patients with a first prescription of amphetamine/dextroamphetamine, methylphenidate, lisdexamfetamine, modafinil, dextroamphetamine sulfate, or cetirizine were identified as cases, with an index date of first prescription and a 365-day washout period without an oral stimulant observable in the cohort. The oral stimulants were prescribed using standard Health Canada dosing guidelines (18). Patients without an eligible prescription of oral stimulants were eligible controls during their follow-up time at the same age and sex as the case patients.

Variables

The study outcome was a positive urinalysis test for cocaine metabolite, defined as a urinalysis threshold value greater than 100 ng/ml (19). Study exposure was the first prescription of oral stimulant.

Covariates included in the analysis were age, sex, and cocaine use history prior to the index date of first oral stimulant prescription with all covariates collected from the electronic medical record. Additional, clinical characteristics were urine drug screening (UDS) results for fentanyl, cannabis, and opioids. Data were collected from identical sources for both exposed and unexposed patients.

Statistical methods

The data were analyzed using descriptive statistics of mean and standard deviation for all demographic, time-dependent confounding and non-independence of observations within and between patients. Random effects were fit for each patient to adjust for the within-patient differences over time (20). Differential follow-up time was implicitly controlled using random effects. Subgroups and interaction effects between covariates were examined using ANOVA for omnibus differences and interclass correlation coefficient matrices (ICC) for pairwise differences in covariates. Time before and after the index event of prescription of oral stimulants was operationalized by calculating the number of days before or after the index event for patients receiving an oral stimulant, and for controls without oral stimulant patients were compared who had been matched on age, sex, and year of cohort entry to cases (**Figure 1**). Three models were fit to analyze the longitudinal data. Model 1 compared patients with an oral stimulant prescription to those without a before and after the index date to compare the association of patients with an oral stimulant prescription to those without before and after a prescription. Model 2 compared patients with an oral stimulant to those without an oral stimulant using post-index date follow-up only (**Figure 2**). Model 3 compared within patient differences among those who received an oral stimulant before and after prescription (**Figure 3**). All fixed effects estimates used a threshold for statistical significance of $p < 0.05$.

Time-to-event models using Kaplan-Meier were fit to assess the time to the first cocaine-positive urine test from the index date of patients receiving an oral stimulant.

Missing data for medications were not present in the dataset because missingness would occur because of lack of collection, not a recorded missing observation. Patient observations with invalid or inconclusive urine tests were excluded and not

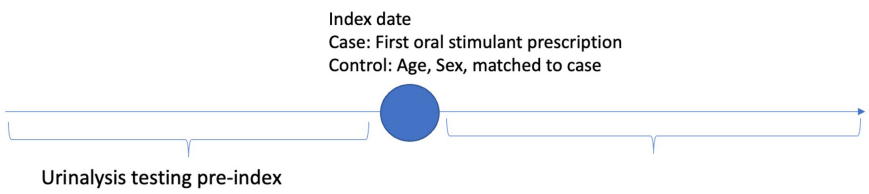

FIGURE 1
Model 1-Pre-post prescription among cases and controls index date.

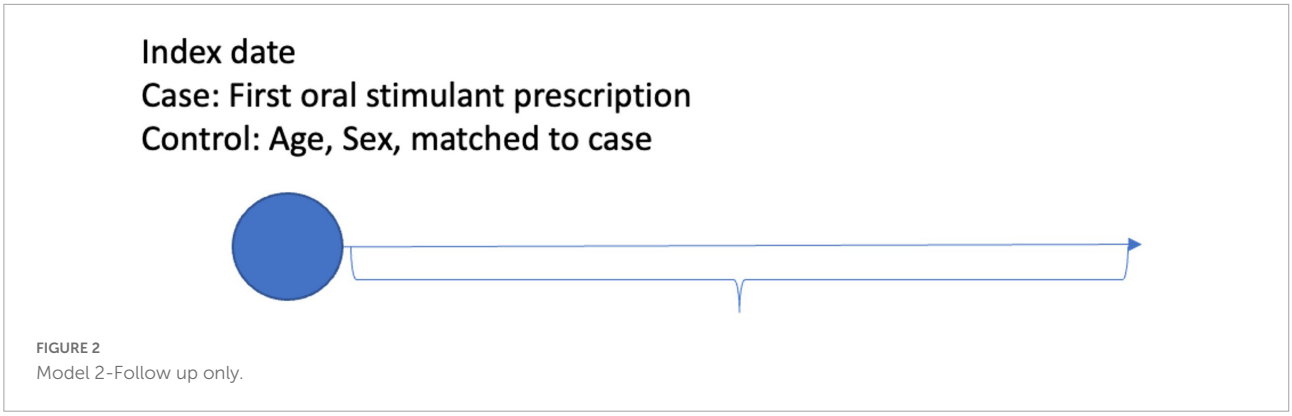

FIGURE 2
Model 2-Follow up only.

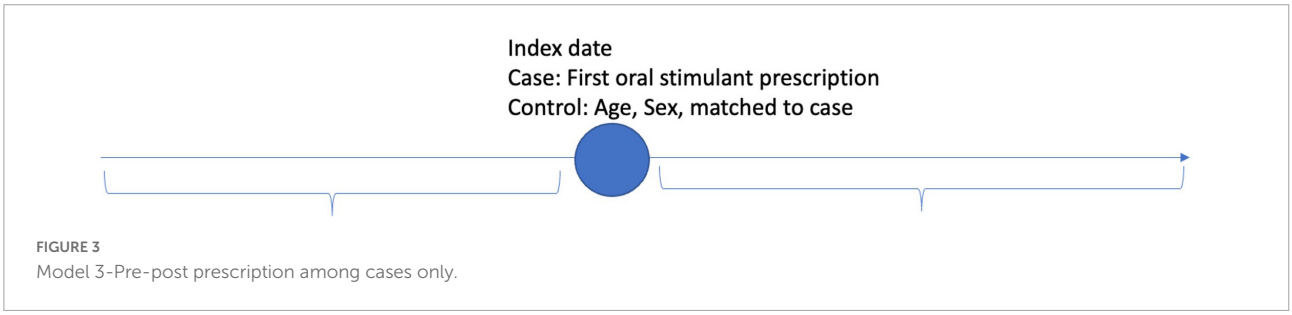

FIGURE 3
Model 3-Pre-post prescription among cases only.

considered missing because these are clinically valid results. No other missing data was present because the database structure requires entry to be complete.

Study ethics were obtained from the research ethics board at the Laurentian University Research Ethics Board. Analysis of data and results were produced using R statistical software version 4.1.1 and the packages lme4 for linear mixed effects models (21). The Strobe Reporting Guidelines 2021 version for observational cohort studies was applied to this study.

Results

Among patients receiving OAT therapy, n = 1,067 patients were prescribed oral stimulants at any time and n = 29,210 patients were not prescribed oral stimulants among Ontario CATC clinics (n = 92, n = 145 physicians). The mean age at enrollment for patients receiving oral stimulants was 37.0, SD = 8.8, with 43.6% female patients and for patients not receiving oral stimulants mean age was 36.6, SD = 10.7, with 39.6% female patients (Table 1). Patients who started in the cohort without an oral stimulant but then received an oral stimulant (n = 314) had 13,043 observed urine tests. Matched non-oral stimulant prescribed controls on age, sex, and year of cohort entry (n = 11,867) had 550,526 observed urine tests (Table 1). Linear mixed effects regression comparing patients with and without prescription of oral stimulants (Model 1) showed no statistical difference in cocaine-positive urine tests before and after prescription (B = 0.00467, SD = 0.00588, P = 0.427) (Table 2). However, when considering the ICC between the fixed effects, we found that time since the prescription of an oral stimulant was associated with a decrease of ICC = −0.09 in cocaine-positive urine tests (Table 3). Examining follow-up data only (Model 2), not adjusting for pre-prescription differences we found a statistically significant increase in cocaine-positive urine tests (B = 0.0873, SD = 0.0162, P < 0.01). Among the patients who received oral stimulants (Model 3), the pre-post analysis showed a non-statistically significant decrease in cocaine-positive urine tests (B = −0.00829, SD = 0.00787, P = 0.292). Within-patient variance values of 0.765 for models 1 and 2 indicate approximately 7% of the variance in outcomes are observed within patients over time. However, the variance within patients increases to 0.0904 among the group receiving oral stimulants only showing greater variance in positive urine tests within patients over time.

Results from the other model predictors indicate that age, and gender, are not associated with cocaine-positive urine tests in any of the models. Time in days after the prescription was found to be statistically significantly associated with cocaine-positive urine tests in models 1 (B = −0.0000534, SD = 4.17E-6, p < 0.01) and model 2 (B = −0.0000603, SD = 4.58E-6, p < 0.01) showing that over time, patients are less likely to test positive for cocaine.

The results of the ICC analysis show that oral stimulants alone (ICCModel 1 = −0.009) and time (ICCModel 1 = −0.033) are both associated with decreasing cocaine-positive urine.

TABLE 1 Patient demographics.

Variable mean (SD)	Exposure	
Exposure group	**Oral stimulant group (n = 314)**	**Control (n = 11,879)**
Patient years of follow-up	173.2	7628.9
Number of urinalysis tests	13,043	550,546
Number of positive tests (%)	4,068 (31.2)	109,492 (19.9)
Urinalysis test per patient	41.54	46.35
Positive tests per patient	12.95	9.21
Age	37.0 (8.8)	36.6 (10.7)
Number female (% female)	137 (43.6)	4,706 (39.6)

However, non-female gender over time was associated with increases in cocaine-positive urine tests (ICC Model 1(male, time) = 0.004). Among patients who received prescriptions for oral stimulants, the male gender was correlated with higher numbers of positive tests over time ICC (male, time) = 0.028.

Kaplan-Meier curves for time to first positive cocaine urine test from the first prescription of oral stimulant showed 29.4% of patients tested positive at 7-days post-prescription, 42.7% positive at 14-days post prescription, and 56.5% positive after 28-days post prescription (Figure 4).

Discussion

This study measured the association of prescription oral stimulant medications on cocaine consumption among a population of patients receiving OAT. As well as to explore the association of prescribed oral stimulants with the retention of OAT. Drawing on longitudinal data from CATC, the largest network of addiction medicine clinics in Canada, using three different statistical models, we found that prescribing oral stimulants to OAT patients was either associated with a small increase or no statistically significant effect in reducing cocaine use. Our results from observational data were unable to confirm clinical trial findings which have shown that prescribing oral stimulants to a small cohort of patients in a controlled setting was associated with reduced cocaine use (15, 22). We sought to test these hypotheses in a real-world setting with a large cohort of patients (n = 12,193) with many observed urine tests (563,589), and patient-years of follow-up (7,802.1). Therefore, our findings may help clinicians with decision-making regarding prescribing oral stimulants to treat cocaine use.

In all statistical models used in this study, we identified correlations with increasing age and time since prescription in reductions in cocaine-positive urine tests. The findings from this study support our previous research and existing literature indicating that concurrent drug use indicates poor outcomes,

TABLE 2 Model results.

	Beta coefficient	Std.	*P-value*
Model 1			
Fixed effects			
(Intercept)	2.54E-01	9.50E-03	<0.01
Time (days)	−5.34E-05	4.17E-06	<0.01
Oral stimulant	4.67E-03	5.88E-03	0.427
Gender (M)	5.70E-03	5.34E-03	0.285
Age (years)	−2.06E-03	2.44E-04	<0.01
Random effects		Variance	Std. dev.
Within patient	(Intercept)	0.07658	0.2767
Residual		7.55E-02	0.2747
Model 2			
(Intercept)	2.54E-01	9.60E-03	<0.01
Time (days)	−.03E-05	4.58E-06	<0.01
Oral stimulant	8.73E-02	1.62E-02	<0.01
Gender (M)	7.41E-03	5.41E-03	0.17
Age (years)	−2.11E-03	2.46E-04	<0.01
Random effects		Variance	Std. dev.
Within patient	(Intercept)	0.07637	0.2763
Residual		7.44E-02	2.73E-01
Model 3			
(Intercept)	2.87E-01	5.88E-02	1.42E-06
Time (days)	−1.17E-05	1.54E-05	0.447
Oral stimulant	−8.29E-03	7.87E-03	0.292
Gender (M)	−1.31E-02	2.68E-02	0.625
Age (years)	−.79E-04	1.52E-03	0.654
Random effects		Variance	Std. dev.
Within patient	(Intercept)	0.09045	0.3008
Residual		0.11023	0.332

TABLE 3 Between covariate interclass correlation coefficient matrix.

	(Intr)	Time (days)	Oral stimulant	Gender (M)
Time (days)	−0.033			
Oral stimulant	−0.009	−0.097		
Gender (M)	−0.229	0.004	0.002	
Age (years)	−0.901	−0.006	−0.001	−0.116
Time (days)	−0.048			
Oral stimulant	−0.044	0.005		
Gender (M)	−0.228	0.003	0.015	
Age (years)	−0.898	−0.011	−0.008	−0.118
Time (days)	0.068			
Oral stimulant	−0.078	−0.407		
Gender (M)	−0.205	0.028	−0.007	
Age (years)	−0.928	0.063	−0.025	−0.059

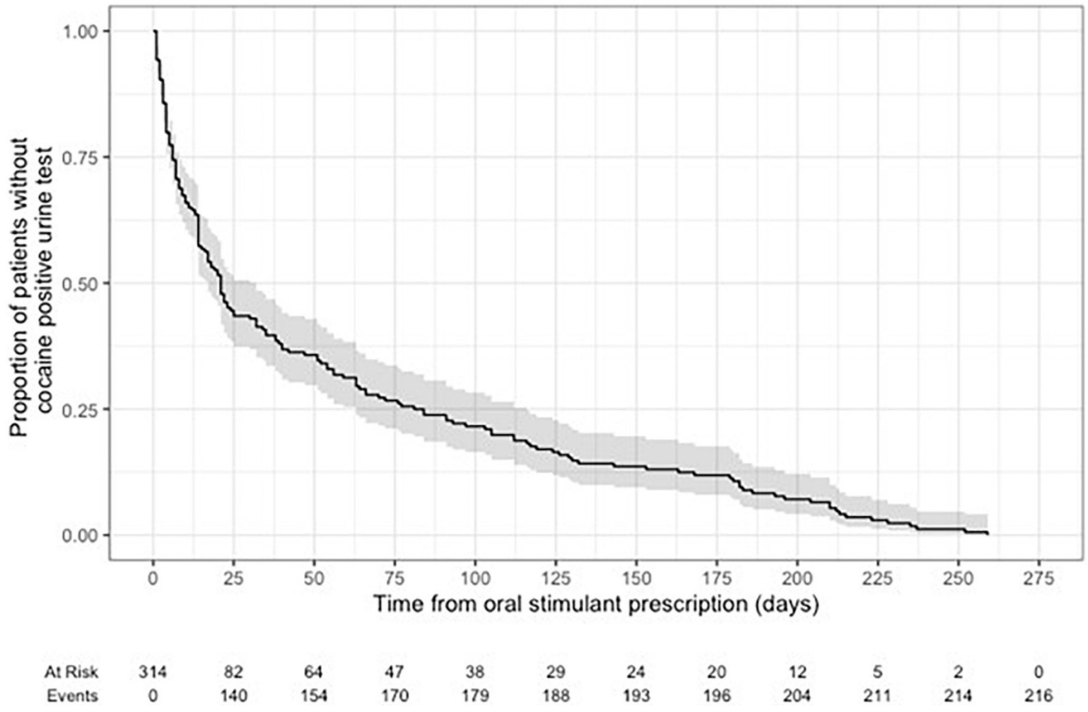

FIGURE 4
Time to first positive cocaine urine test from the first prescription of oral stimulant.

but that the effect is reduced with increased time in treatment (4, 7, 23).

Our ICC model also indicated that, among patients who received prescriptions for oral stimulants, the male gender was correlated with higher numbers of positive tests over time. This observation also aligns with the literature indicating that the prevalence of stimulant use is higher among males (22–24). This observation is particularly important in the era of increased exposure to synthetic opioids such as fentanyl, treatment retention has been declining (25–27). OAT has become more accessible to high-risk patients, including those who continue to use cocaine while in treatment (1, 10, 28). Therefore, the decreasing retention may not be reflective of the effectiveness of OAT, but a reflection of the changing needs of this population. Understanding the changing needs of the OAT population may help clinicians and policymakers in planning and recommending more patient-centered interventions.

The first statistical model used in this study compares patients with a prescription of oral stimulant to those without, before, and after the prescription index date. Our analysis shows that patients with an oral stimulant prescription test positive for cocaine more often per unit of time, compared to those without an oral stimulant in the pre-prescription time period but these results did not meet the threshold of statistical significance. We then wanted to examine if removing controls for past cocaine use increased the differences between the stimulant prescribed and control groups. Therefore, ignoring the pre-existing cocaine-positive test differences between the two groups in the second model, we showed that the difference between oral stimulants prescribed patients and non-oral stimulant patients was statistically significantly different in follow-up only. Our third model restricted the analysis to patients receiving an oral stimulant using a pre-post prescription analysis, to show the association of prescription on pre and post-prescription cocaine-positive urine tests. In this case, we found no statistically significant difference meaning the oral stimulant prescription had no association on change in cocaine-positive urine before compared to after prescription.

Our results suggest the oral stimulant intervention has no detectable effect on cocaine use in a real-world setting. It is possible that this subgroup of OAT patients experiences more exposure to physiological and social events that trigger increased drug use, and that there may not be a quick solution to reducing the use of cocaine. Large scale meta-analysis and systematic reviews have shown that patient outcomes improve when the complete package of treatment are included in the treatment of substance use disorders such as contingency management approaches to take-home doses of OAT, psychosocial supports, services to address concurrent mental and physical health, trauma-informed and culturally appropriate services (13, 29). Therefore, more research is needed

to explore effective treatment options for higher-risk patients enrolling in OAT, such as those included in this study.

Some limitations in the current study require attention. First, there is a possibility of data entry and reporting errors associated with using secondary data. Second, the data is collected for purposes other than research, therefore we were limited to using the data which is routinely collected. Third, although we considered various factors in our statistical models, there is potential for unmeasured confounding, including confounding related to social and interpersonal factors, lack of measurement of addiction severity and some clinical characteristics. Lastly, because of the challenge in diagnosing ADHD in the presence of active cocaine use, and absence of standardized testing for ADHD in a searchable format within the EMR, we have included all patients prescribed oral stimulants while on OAT. We are not able to stratify asked on presence or absence of ADHD symptoms but all the prescriptions have been done with the goal of decreasing cocaine use.

Conclusion

The use of oral stimulant prescription among patients receiving OAT showed no statistically significant difference in cocaine consumption in a real-world setting, despite modest positive effect sizes demonstrated in previously conducted clinical trials. This finding highlights the value of further investigation and understanding of the needs of patients who use cocaine while in OAT. We also observed that cocaine use was reduced with increased time since treatment initiation. Given the high rates of cocaine use among patients in OAT, our findings are important to help clinicians make informed decisions about appropriate treatments and to increase OAT retention for this group of patients. Our findings suggest a need to develop a more comprehensive strategy to treat people with concurrent substance use and opioid use disorders to maximize the benefits of OAT.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The datasets used during the current study are not publicly available due to privacy reasons, but aggregated data are included in this published article. Requests to access these datasets should be directed to MT, tatangelomark@gmail.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Laurentian University Research Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MT participated in the data acquisition, conceptualization, data analysis, and final revision of the manuscript. FT participated in the conceptualization, writing of the original draft, revisions, and final revision of the manuscript. KM participated in the conceptualization, study design, supervision, and final revision of the manuscript. DM played a leadership role in the planning of the study, contributed to the interpretation of results, and final review of the manuscript. FT and KM contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

Author DM maintained the following roles from 2014 to July 2022: Chief Medical Director at CATC (Canadian Addiction Treatment Center), and opioid agonist therapy provider. Author DM had no ownership stake in the CATC as a stipendiary employee.

The remaining 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.

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Effect of short-term mindfulness-based stress reduction on sleep quality in male patients with alcohol use disorder

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Background: Sleep disturbance is one of the most prominent complaints of patients with alcohol use disorder (AUD), with more than 70% of patients with AUD reporting an inability to resolve sleep problems during abstinence. Mindfulness-based stress reduction (MBSR) has been shown to improve sleep quality and as an alternative therapy to hypnotics for sleep disorders.

Objective: The aim of the present study was to evaluate the effect of short-term MBSR on sleep quality in male patients with AUD after withdrawal.

Methods: A total of 91 male patients with AUD after 2 weeks of routine withdrawal therapy were randomly divided into two groups using a coin toss: the treatment group ($n = 50$) and the control group ($n = 41$). The control group was received supportive therapy, and the intervention group added with MBSR for 2 weeks on the basis of supportive therapy. Objective sleep quality was measured at baseline and 2 weeks after treatment using the cardiopulmonary coupling (CPC). Indicators related to sleep quality include total sleep time, stable sleep time, unstable sleep time, rapid eye movement (REM) sleep time, wake-up time, stable sleep latency, sleep efficiency, and apnea index. These indicators were compared by an analysis of covariance (ANCOVA) between the two groups, controlling for individual differences in the respective measures at baseline.

Results: The results showed that there were no significant differences in the age [t (89) = −0.541, $P = 0.590$), BMI [t (89) = −0.925, $P = 0.357$], educational status [t (89) = 1.802, $P = 0.076$], years of drinking [t (89) = −0.472, $P = 0.638$), daily intake [t (89) = 0.892, $P = 0.376$], types of alcohol [χ^2 (1) = 0.071, $P = 0.789$], scores of CIWA-AR [t (89) = 0.595, $P = 0.554$], scores of SDS [t (89) = −1.151, $P = 0.253$), or scores of SAS [t (89) = −1.209, $P = 0.230$] between the two groups. Moreover, compared with the control group, the total sleep time [F (1.88) = 4.788, $P = 0.031$) and stable sleep time [F (1.88) = 6.975, $P = 0.010$] were significantly increased in the treatment group. Furthermore, the average apnea index in the patients who received MBSR was significantly decreased than in the control group [F (1.88) = 5.284, $P = 0.024$].

Conclusion: These results suggest that short-term MBSR could improve sleep quality and may serve as an alternative treatment to hypnotics for sleep disturbance in patients with AUD after withdrawal.

KEYWORDS

cardiopulmonary coupling, sleep quality, apnea index, alcohol use disorder, mindfulness-based stress reduction

1. Introduction

According to the 2018 World Health Organization Global status report on alcohol and health, the harmful use of alcohol is responsible for ~3 million deaths, accounting for nearly 5.3% of the global deaths due to disease in 2016 (1). Beyond health problems, the harmful use of alcohol imposes high social and economic costs on society (2). Due to the fact that approximately 90% of patients with alcohol use disorder (AUD) experience at least one relapse over a 4-year period after treatment, reducing the craving and recurrence rate is of great clinical significance (3).

Sleep disturbance is one of the most prominent complaints of alcohol-dependent patients, with more than 70% of patients with AUD reporting an inability to resolve sleep problems during abstinence (4). Accumulated data support a bidirectional relationship between alcohol craving and sleep disturbance (5–9). It has been reported that alcohol negatively affects sleep quality by decreasing the rapid eye movement (REM) sleep phase and the total sleep time (10). On the contrary, patients with obstructive sleep apnea are at a higher risk of developing alcohol-related diseases (8). Most alcohol-dependent patients may use alcohol to self-medicate sleep disturbance (11). Given that sleep disturbance is associated with negative consequences such as decreased quality of life, poor work performance, and mood and anxiety symptoms, improving sleep quality in alcohol recovery may provide an easily identifiable treatment target and potentially improve long-term outcomes of alcohol dependence. However, treatment options for sleep disorders in patients with AUD are limited, and there may be risks due to abuse/overdose associated with some hypnotics (12).

Mindfulness meditation was developed to help individuals manage stress or illnesses by combining meditation with mindfulness skills training (13). Growing evidence supports the benefits of meditation for ameliorating sleep quality (14–17). Mindfulness-based stress reduction (MBSR), a standardized stress reduction program that emphasizes mindfulness meditation, has recently been shown to significantly improve sleep disturbance symptoms in several diseases, including cancers, cirrhosis, and insomnia (18–21). However, to our knowledge, few studies have evaluated the potential therapeutic effect of MBSR on sleep disturbances in patients with AUD. Given the good safety and potential therapeutic effects on sleep quality, MBSR may be a useful, non-pharmacological, and non-invasive method with a beneficial impact on the sleep management of patients with AUD.

Considering the close relationship between sleep disturbance and negative consequences of AUD (22, 23), together with the potential therapeutic effect of MBSR on sleep quality, the aim of the present study was to investigate the effect of short-term MBSR on sleep quality in male patients with AUD after withdrawal.

2. Materials and methods

2.1. Subjects

The study was conducted between October 2019 and October 2020 at the Affiliated Psychological Hospital of Anhui Medical University. A total of 91 male patients with a diagnosis of AUD were included as per the International Classification of Diseases 10th Revision Diagnostic Criteria for Research (ICD-10 DCR) criteria. All the patient subjects conformed to the following inclusion criteria: (1) male inpatients; (2) age 18–65 years; (3) Han Chinese ethnicity; (4) completion of benzodiazepines substitution. Patients with any of the following were excluded from this study: (1) any comorbid psychiatric disorders (e.g., psychosis, schizophrenia, bipolar disorder, panic disorder, and obsessive–compulsive disorder) or active suicidal ideation (moderate or high suicidality); (2) diagnosed with a substance-dependent disorder other than alcohol; and (3) diagnosed with a serious neurological or medical condition. In accordance with the principles of the Declaration of Helsinki, all subjects provided informed written consent prior to participation. The Ethics Committee of Hefei Fourth People's Hospital, Anhui Mental Health Center, approved this study.

2.2. Demographic and clinical data collection

A Demographics Questionnaire was used to collect general information about participants, such as sex, age, body weight, height, body mass index (BMI), years of education, marital status, years of drinking, daily intake, and types of alcohol by face-to-face interview. The severity of alcohol withdrawal was measured by the Clinical Institute Withdrawal Assessment-Alcohol, Revised (CIWA-AR), which is a 10-item measure used to provide a quantitative index of the severity of the alcohol withdrawal syndrome. The most common mental health comorbidities associated with AUD were anxiety and depression disorder (24). The Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) were used to assess the degree of anxiety and depression, respectively.

2.3. Study design

A total of 91 male patients with AUD were enrolled. These patients all underwent an alcohol dependence rehabilitation treatment program for 1 month, including 1-week detoxification and 3-week supportive therapy, such as correction of electrolyte imbalance, liver-protecting therapy, and vitamin B supplementation. All patients should meet the conditions of receiving detoxification replacement therapy to reduce dependence (1 week) and be in a stable alcohol withdrawal period at the time of enrollment before MBSR treatment. At the end of the 2nd week of the treatment program, they were randomly divided into two groups using a coin toss: the treatment group ($n = 51$) and the control group ($n = 40$). The control group received supportive therapy, and the treatment group was provided with MBSR for 2 weeks on the basis of supportive therapy. The training was conducted once a day for 45 min, 5 times/week, for 2 weeks. Before the first intervention, the trained nurses introduced the meditation in detail, including the theoretical knowledge, efficacy, and precautions of meditation training, to ensure that each patient was clear and mastered the training procedure. The patients were placed in a sound insulation room with a constant temperature

of 25°C and asked to sit upright with their backs against the backrest of an armless chair. The procedures of meditation were as follows: The trained nurses used simple instructions to lead the patients to experience a meditative state of concentration for 10 min and then played a series of meditation music to guide the patients to conduct a 35-min meditation relaxation training: (1) focus on breathing and make it deep and long; (2) completely relax the muscles of the whole body from head to feet; (3) feel any subtle changes in mind, and experience the changes of the body from feet to head; (4) imagine pleasant things or scenes to completely relax body and mind; and (5) slowly open eyes and end the meditation (for a more detailed script of the MBSR, see Supplementary Table S1). Objective sleep quality was measured at baseline and 2 weeks after treatment using the cardiopulmonary coupling (CPC; Fengshengyongkang Software Technology Ltd., Co., Nanjing, Jiangsu Province, China). Figure 1 illustrates the summary of the participants' screening and enrollment processes.

2.4. CPC analysis

The CPC technique is based on a continuous single-lead electrocardiogram (ECG) signal and uses the Fourier transform to extract heart rate variability and ECG-derived respiration (EDR) activity from the ECG signal. Sleep stability and the presence of sleep-disordered breathing can be obtained from the connected software by calculating the cross-power and coherence between the two signals. Specifically, high-frequency coupling (frequency range of 0.1–0.4 Hz) represents stable sleep; low-frequency coupling (frequency range of 0.01–0.1 Hz) represents unstable sleep; very-low-frequency coupling (frequency range of 0.001–0.01 Hz) represents wakefulness or rapid eye movement sleep; elevated-low frequency coupling represents apnea index [specifically, the detection of elevated-low-frequency coupling requires that the minimum low-frequency power be >0.05 normalized units and that the low to high-frequency ratio be >30 to define periods of probable apnea/hypopnea (25). The apnea index defines as the average number of apneas and hypopneas occurrences per hour].

2.5. Statistical analysis

The data were analyzed using SPSS (Version 17.0; SPSS, Inc, Chicago, IL, USA). The differences in the demographic and clinical characteristics were analyzed using Student's *t*-test or χ^2 test between groups. After a 2-week treatment, an analysis of covariance (ANCOVA) was performed to compare the indicators related to sleep quality, including total sleep time, stable sleep time, unstable sleep time, REM sleep time, wake-up time, stable sleep latency, sleep efficiency, and apnea index between groups, controlling for individual differences on the respective measures at baseline. An interaction term between the group and the covariate was initially included to check the parallelism assumption, and all the interactions were not significant. A *P*-value of <0.05 (two-tailed) was considered statistically significant.

A sensitivity analysis using G-power software (Version 3.1.9.2 Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany) (26) indicated that, given α of 0.05 and power (1-β) of 0.80, a study with two groups and a total sample size of 91 would be able to detect an effect size (f) of 0.30 with fixed effects, main effects and interactions ANCOVA (noncentrality parameter λ = 8.02; critical F = 3.95; denominator df = 88). Using Cohen's (27) effect size guidelines of $f = 0.10$ as small, $f = 0.25$ as medium, and $f = 0.40$ as large, our sample size was sufficient to detect medium effect sizes. Therefore, the study is sufficiently powered to detect moderate differences in the CPC-based sleep quality between groups.

3. Results

3.1. Demographic and clinical characteristics of the treatment and control groups

As shown in Table 1, there were no significant differences in the age (t (89) = −0.541, P = 0.590), BMI (t (89) = −0.925, P = 0.357), educational status (t (89) = 1.802, P = 0.076), marital status (χ^2 (1) = 1.745, P = 0.186), years of drinking (t (89) = −0.472, P = 0.638), daily intake (t (89) = 0.892, P = 0.376), types of alcohol (χ^2 (1) = 0.071, P = 0.789), scores of CIWA-AR (t (89) = 0.595, P = 0.554), scores of SDS (t (89) = −1.151, P = 0.253), or scores of SAS (t (89) = −1.209, P = 0.230) between the two groups.

3.2. Effects of short-term MBSR on the CPC-based sleep quality in patients with AUD

The total sleep time of the control group and the treatment group at baseline was (6.91 ± 0.29) h and (6.81 ± 0.22) h, respectively. After 2-week treatment, the results of the ANCOVA showed that compared with the control group, the total sleep time in the treatment group was significantly higher (F (1.88) = 4.788, P = 0.031, Figure 2A).

The stable sleep time of the control group and the treatment group at baseline was (2.98 ± 0.26) h and (2.41 ± 0.22) h, respectively. After the treatment, the stable sleep time in the patients who received MBSR was significantly higher than that in the control group [F (1.88) = 6.975, P = 0.010, Figure 2B].

The unstable sleep time of the control group and the treatment group at baseline was (2.51 ± 0.18) h and (2.88 ± 0.18) h, respectively. After the treatment, there was no difference in unstable sleep time [F (1.88) = 1.241, P = 0.268, Figure 2C] between the two groups.

The REM sleep time of the control group and the treatment group at baseline was (1.45 ± 0.15) h and (1.54 ± 0.09) h, respectively. After the treatment, there was no difference in the REM sleep time [F (1.88) = 0.810, P = 0.371, Figure 2D] between the two groups.

The wake-up time of the control group and the treatment group at baseline was (1.06 ± 0.09) h and (1.07 ± 0.10) h, respectively. After the treatment, no difference in the wake-up time was found between the two groups [F (1.88) = 0.105, P = 0.747, Figure 2E].

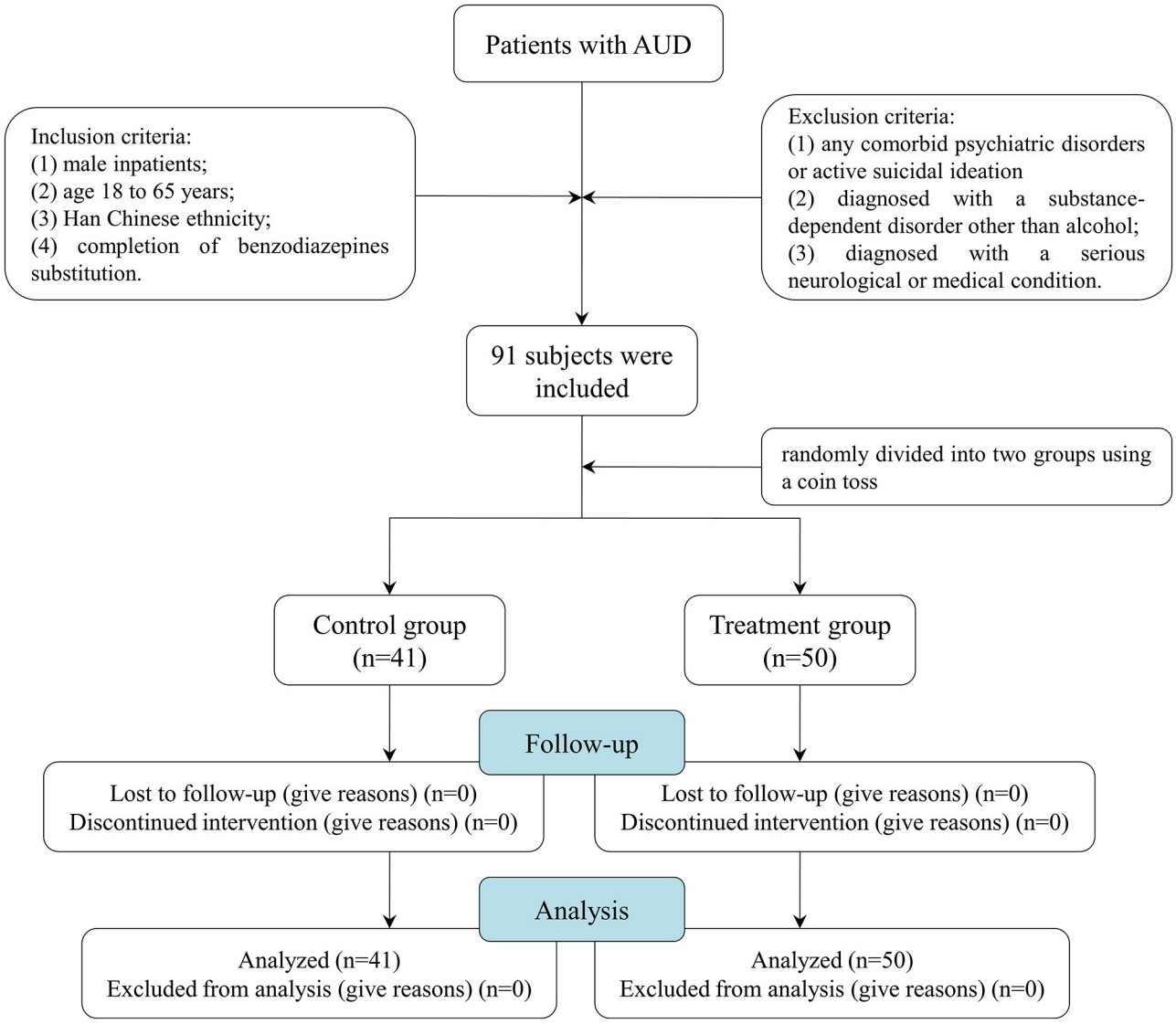

FIGURE 1
Flowchart showing the enrollment process for participants.

The stable sleep latency of the control group and the treatment group at baseline was (79.85 ± 19.17) min and (95.82 ± 14.67) min, respectively. After the treatment, no difference in the wake-up time was found between the two groups [F (1.88) = 0.184, P = 0.669, Figure 2F].

The sleep efficiency (ratio of total sleep time to total in-bed time) of the control group and the treatment group at baseline was (79.75 ± 2.48)% and (81.55 ± 1.70)%, respectively. After the treatment, no difference in the wake-up time was found between the two groups [F (1.88) = 2.387, P = 0.126, Figure 2G].

The apnea index (average number of apnea occurrences per hour) of the control group and the treatment group at baseline was (12.08 ± 2.76) events/h and (16.74 ± 2.48) events/h, respectively. After the treatment, the apnea index in the treatment group was significantly lower than that in the control group [F (1.88) = 5.284, P = 0.024, Figure 2H].

4. Discussion

Accumulating evidence indicates that MBSR has the potential to improve sleep quality cancers, cirrhosis, and insomnia (18–21, 28). To our knowledge, this is the first study to analyze the effects of MBSR on sleep quality in patients with AUD. The main finding is that 2-week MBSR increased the total sleep time and stable sleep time and decreased the apnea index in patients with AUD, suggesting the potential therapeutic effect of short-term MBSR on sleep disturbance in patients with AUD after withdrawal.

Cardiopulmonary coupling is a spectroscopic method developed as an alternative to polysomnography to quantify sleep quality (29). The CPC technique is based on a continuous single-lead electrocardiogram (ECG) signal to track changes in cardiac inter-beat (R-R) intervals and QRS amplitude during sleep (25). Since CPC analysis has several advantages, such as objectivity,

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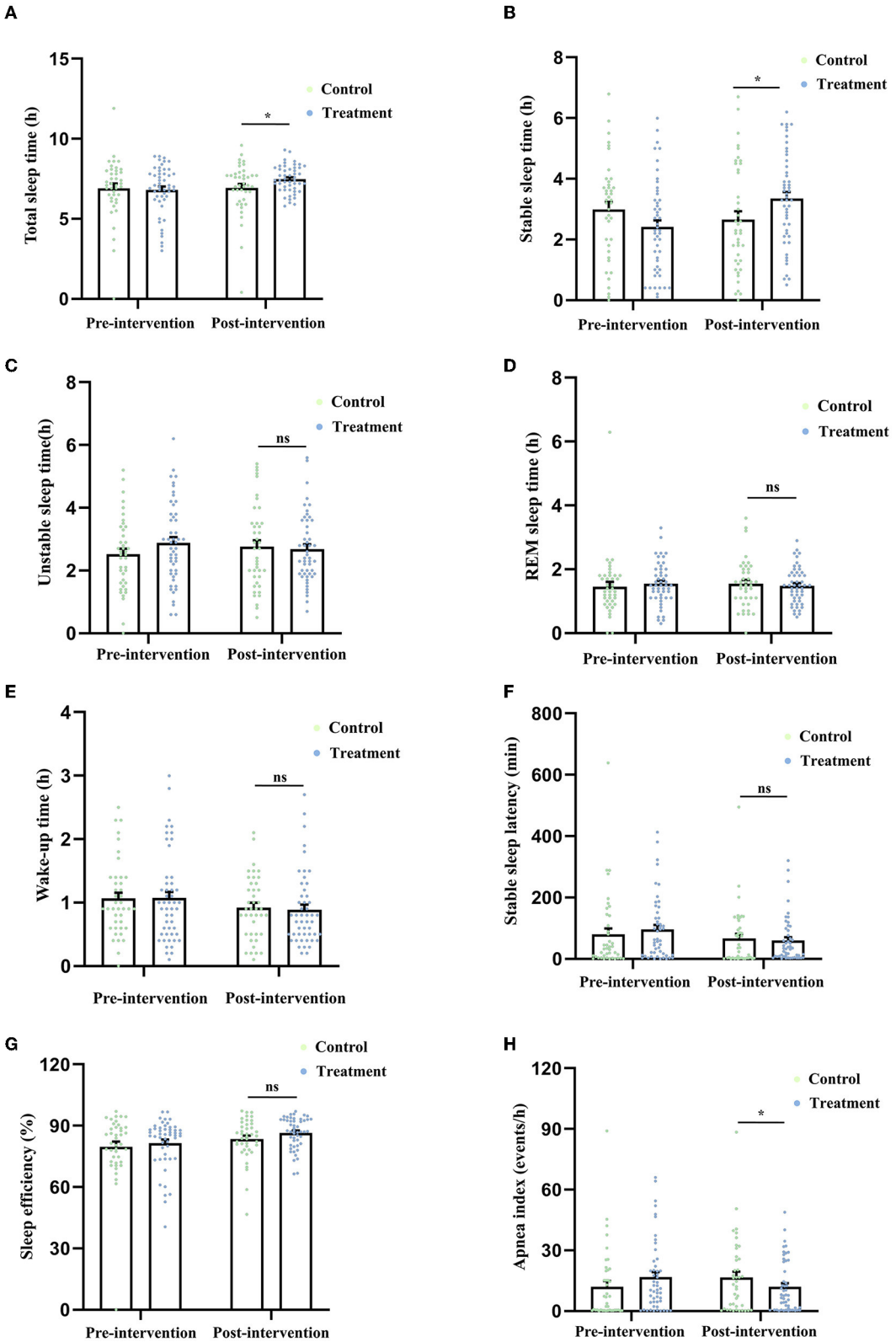

FIGURE 2
Comparison of the indicators related to sleep quality derived from the CPC technique, including total sleep time **(A)**, stable sleep time **(B)**, unstable sleep time **(C)**, REM sleep time **(D)**, wake-up time **(E)**, stable sleep latency **(F)**, sleep efficiency **(G)**, and apnea index **(H)** between the two groups after 2-week treatment. *$P < 0.05$ was considered statistically significant. ns, no significance.

TABLE 1 Comparison of demographic and clinical data in the treatment and control groups (mean ± SEM).

Variables	Control group	Treatment group	Statistics (t/χ^2)	*P*
Age	44.10 ± 1.48	45.18 ± 1.35	−0.541	0.590
BMI (kg/m²)	21.80 ± 0.56	22.47 ± 0.47	−0.925	0.357
Educational status (years)	10.07 ± 0.53	8.88 ± 0.39	1.802	0.076
Marital status			1.745	0.186
Married	34	46		
Single/divorced/separated	7	4		
Years of drinking	20.16 ± 1.66	21.18 ± 1.41	−0.472	0.638
Daily intake (standard drink)	9.51 ± 0.52	8.74 ± 0.72	0.892	0.376
Types of alcohol			0.071	0.789
Wine	36	45		
Wine + Beer	4	6		
CIWA-AR	6.67 ± 0.73	6.03 ± 0.76	0.595	0.554
SDS	42.03 ± 1.60	44.85 ± 1.86	−1.151	0.253
SAS	38.16 ± 1.56	40.80 ± 1.51	−1.209	0.230

repeatability, automation, and scorer-independence (30), it has been widely used to evaluate sleep quality in several diseases, including Parkinson's disease (31), depression (32), and obstructive sleep apnea (33). Therefore, CPC was chosen to measure sleep quality in the present study.

Several lines of evidence have suggested that MBSR is proposed as an adjunctive treatment targeting relapse prevention in substance use disorders (34), the mechanisms of which may be related to improved emotion regulation, reduced stress reactivity, and decreased risk of relapse in high-risk situations (35, 36). In terms of AUD, several studies of mindfulness-based interventions have shown beneficial findings for risks of relapse and the severity of depression, anxiety, and stress symptoms (37–39). However, to the best of our knowledge, few studies examine the effects of MBSR on sleep quality in patients with AUD. The results of the present study indicated that short-term MBSR as an adjunct to usual care showed to improve sleep disturbance in alcohol-dependent patients in early recovery compared to usual care alone, providing a novel potential mechanism for MBSR as an adjunctive therapy for patients with AUD.

Sleep continuity includes total sleep time, stable sleep time, sleep latency, sleep efficiency, and wake after sleep onset. Among them, stable sleep is characterized by the absence of respiratory abnormality or progressive flow limitation and usually demonstrates non-CAP EEG (40). Numerous studies have confirmed disturbances of sleep continuity in patients with AUD (41–43). Specifically, patients with AUD showed difficulty in falling asleep, decreased total sleep time, and decreased sleep efficiency after acute abstinence, predicting the likelihood of relapse during longer periods of abstinence (44). In the present study, 2-week MBSR was found to increase the total sleep time and stable sleep time in alcohol-dependent patients after withdrawal, suggesting that short-term MBSR could improve the disturbances of sleep continuity in patients with AUD.

Sleep apnea, characterized by recurrent upper airway obstruction during sleep, is associated with arterial blood desaturation, sympathetic nervous system activation, and cardiovascular impairment (45, 46). The apnea index is an indicator of the severity of sleep apnea, which measures the hourly occurrence rate of apneas and hypopneas (47). Previous studies have indicated that alcohol dependence is associated with sleep apnea. Alcohol has been shown to relax the upper airway while reducing the normal arousal response to airway obstruction, leading to impaired normal breathing, such as sleep fragmentation and sleep-disordered breathing (10, 48). A recent study has demonstrated a significant independent association of dispositional mindfulness with continuous positive airway pressure (CPAP) (49), a standard treatment for obstructive sleep apnea. Taken together, the results of the present study show that the apnea index was significantly decreased in patients with AUD who received MBSR compared with control subjects; it is rational to presume that MBSR may be a potential treatment option for sleep apnea in male patients with AUD after withdrawal.

The following medications are currently Food and Drug Administration (FDA) approved for the treatment of sleep disorders: benzodiazepines and non-benzodiazepine hypnotics, tricyclic antidepressants, therapeutic drugs that target orexin/hypocretin receptors, and off-label use of medications such as other antidepressants, antihistamines, herbal preparations, and antipsychotics (50–52). However, these medications, including benzodiazepines and other hypnotics, might not be appropriate for treating sleep disturbance in AUD due to their potential for addiction and side effects, which can include residual sedation, memory and performance impairment, unwanted behaviors while sleeping, somatic symptoms, and drug interactions (53). Over more conventional types of treatment for sleep disorders, mindfulness-based therapies may offer a number of significant benefits: (1) mindfulness-based interventions can be given in a group setting over a short-term period, making them cost-effective;

(2) MBSR is generally free of unwanted side effects and can be applied across a wide range of populations and disorders; and (3) attending a mindfulness class rather than engaging in other types of mental health therapy seems to be perceived by many individuals as having fewer stigmas. Thus, taken together, the results of the present study, MBSR may serve as an alternative treatment to hypnotics for sleep disturbance in patients with AUD.

There were several limitations to our study. First, the current study is a single-center study with a small sample size. Second, since the vast majority of Chinese patients with AUD are male patients, our hospital has only set up male inpatient areas. Thus, only male patients with AUD were included in the present study. The inability to examine gender differences may be considered a limitation. Third, the long-term effect of MBSR on the sleep quality of alcohol-dependent patients after withdrawal was not observed. Fourth, we cannot rule out the effect of the participants' mere time spent with experts on the results. It may be appropriate to add the same participants' mere time spent with experts in the control group to eliminate the influence of this unspecific factor.

At the end of this study, we concluded that short-term MBSR could improve sleep quality and may serve as an alternative treatment to hypnotics for sleep disturbance in patients with AUD after withdrawal. The exact mechanism and long-term effects of MBSR need further study to explore.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Hefei Fourth People's Hospital, Anhui Mental Health Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW, CC, LP, and LX designed the study and wrote the protocol and the first draft of the manuscript. YW, CC, LG, YZ, YS, and GG performed the experiments. YX managed the literature searches and the statistical analyses. LP and LX edited the manuscript. All authors contributed to and have approved the final manuscript.

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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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.928940/full#supplementary-material

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Study protocol: the pragmatic, exploratory DELTA-JU trial of the group-based multimodal DELTA intervention for abstinent adolescents with substance use disorders living in youth welfare institutions

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Background: The DELTA intervention contains 16 weekly group sessions plus additional individual sessions and educational session for parents. It aims to reduce substance use and related problems such as substance use disorders (SUD) in adolescents. Recent results indicated positive effects in psychiatric outpatients. Conducting DELTA in youth welfare settings seems feasible, however, organizational and content adjustments such as smoking cessation elements should be added in order to reduce relapse risks and to prevent negative health consequences.

Methods/design: The pre-registered DELTA-JU study (German Clinical Trials Register, DRKS00027913) is separated into three stages: In the adjustment stage during months 1–4, we will revise the DELTA manual based on semi-structured interviews (n =10) with personnel from youth welfare institutions specialized in serving adolescents with SUD in the study region, analyzed with content analysis. In the sampling stage during months 5–22, participants qualifying for a SUD and willing to regularly participate in the 16 weekly DELTA-JU group sessions will be enrolled to either one of two arms (cluster randomization: immediate intervention, waitlist with subsequent intervention 16weeks later). Adolescents will be assessed at baseline and follow-up (16weeks after first group session) with an additional pre-assessment (16weeks before intervention starts) for the waitlist group. Assessment procedures include questionnaires and clinical interviews among others. At the same time, institutional personnel will receive a 1-day workshop on SUD-relevant topics based on the DELTA parental education group and on feedback from the qualitative interviews. Personnel will also be assessed twice with questionnaires. In the dissemination stage during months 23–24, final study evaluation results will be prepared and submitted for publication.

Discussion: This study will create a setting-specific manual for vulnerable adolescents suffering from SUDs, and, in many cases, from co-occurring mental disorders. If shown to be effective, DELTA-JU can be disseminated within other institutions of youth welfare.

KEYWORDS

addiction, clinical trial, dependence, drug abuse, recovery, therapy, treatment, waiting list control group

Introduction

Adolescents aged 12–18 years are likely to experiment with psychoactive substances such as alcohol and cannabis (1), with 2–10% of those who use substances developing a substance use disorder (SUD) over the course of the next years (2). SUDs are characterized as chronic mental disorders that tend to relapse into episodes of heavy substance use based on a set of biopsychosocial relapse determinants (3, 4). Such factors not only increase the risk for relapse, they are also prevalent among SUD outpatients. In our own sample of 204 outpatients (5), the majority qualified for more than one SUD (67%), had lived in single-parenthood homes (84%), repeated a class or left school prematurely (53%), or reported previous suicidal attempts (23%). Consequently, untreated SUDs are associated with delayed psychosocial development (6) and increased mortality (7, 8), thus indicating a need for prevention and treatment of SUDs.

In order to extend the existing treatment options for adolescents in Germany (9–11), we previously developed a multimodal, group-based outpatient intervention. This "Dresden multimodal therapy for adolescents with chronic substance use" (German abbreviation: DELTA) (12), consists of 16 structured weekly sessions in a group setting plus eight 1-on-1 sessions and eight additional education sessions for patients' parents. DELTA combines recommended psychotherapeutic techniques and approaches such as motivational interviewing, contingency management, and cognitive-behavioral and systemic therapy, while also addressing mental disorders which commonly occur in addition to SUDs (5, 13, 14).

Research directions regarding the DELTA manual

In our recent presentation of DELTA evaluation data in $N = 146$ psychiatric outpatients (including participants from youth welfare institutions), we presented first evidence that the DELTA intervention for adolescents with SUD is feasible, and shows small to medium non-significant effects in favor of DELTA regarding a reduction of both SUD severity and substance use at approximately 8 weeks after the last group session (15). Additionally, we found (small to medium) effects on the reduction of the depressive symptoms, understanding and influencing aversive emotions, and promoting prosocial behavior.

This power problem also precluded us from analyzing differences in treatment effects comparing outpatients at our outpatient unit with those who resided in a youth welfare institution and received DELTA there. Therefore, we can only assume that DELTA works the same way and leads to similar results in both settings. However, those settings differ from each other significantly. For example, in the outpatient institution, participants have to organize their commute to the group sessions while in youth welfare institutions, participants do not have to leave the building. Youth welfare institutions promote participation in group session as they schedule the group in accordance with their internal schedules, which is in contrast to the afternoon group slot in our outpatient facility which is at the same time where participants want to spend their free time with their peers. Based on these setting differences, we decided to gather additional data on DELTA in youth welfare settings where less than 33% of previously analyzed participants were treated.

Setting specifics in content

In our outpatient facility, adolescents may or may not yet have reached abstinence at the beginning of treatment (15). Thus, DELTA aimed at reducing substance use, achieving point abstinence, and finally achieving continuous abstinence (12). The initial sessions therefore focus on motivational techniques to reinforce commitment to achieve abstinence. In contrast, those in youth welfare institutions generally are abstinent with the start of their stay (15). In most cases they underwent inpatient detoxification before being transferred to the youth welfare institution. Thus these adolescents may already have gained SUD-related knowledge ("subjective utility") and may already be motivated to remain abstinent rather than becoming abstinent. Not surprisingly, the evaluation study showed lowest satisfaction of adolescents with content regarding "strategies to reduce fear, to increase SUD-related subjective utility, and to reignite self-confidence in patients" (15). Therefore, it seems adequate to reframe respective sessions to fit setting-specific needs. Adolescents in these institutions live there full-time following structured routine involving psychological care, schooling, household chores, exercise, and other activities. They are under supervision continuously and are only allowed on weekends depending on their participation and commitment to institutional rules. Medical care (including psychiatric medication) is not provided by internal staff but is accessed the same ways as for other adolescents (appoints at external institutions/psychiatrists).

Setting specifics in stakeholder education

In the outpatient facility, adolescents present with their parents or legal guardians whom they reside with in most cases. These adults are important stakeholders in the treatment process (16, 17). Previous studies showed that parents of adolescents with SUD are both suffering from the situation but may also help to achieve treatment goals (18, 19). Thus, DELTA provided a parental education

Abbreviations: BL/FU/PRE, Assessments during the study at baseline, follow-up or previous to baseline; DRKS, German Clinical Trials Register; DELTA, Dresden multimodal therapy for adolescents with chronic substance use (German abbreviation); DELTA-JU, The revised DELTA program for youth welfare institutions (JU=in Jugendwohneinrichtungen in German); ICMJE, International Committee of Medical Journal Editors; ID, Personal identification number used to anonymize study data; MANOVA, Multivariate analysis of variance; SPIRIT, Standard protocol items: recommendations for interventional trials; SUD, Substance use disorders; WL, Waiting list control group (study arm/condition).

group, with eight 60-min sessions providing expert input (substances, SUD development, treatments, and family processes) as well as opportunities to reflect and discuss with other parents. In the youth welfare setting, parents do not reside with the adolescents. Although parental education settings were offered in all cooperating youth welfare institutions, the vast majority of parents generally did not attend them nor did they express interest. From a systemic perspective, institution personal plays the role of a quasi-parent in these settings. Institutional personnel may provide comparable involvement and effects in relation to the adolescent's SUD and treatment. Thus, a revised DELTA manual should prepare similar educational sessions but for personnel. Based on feedback from the institutions during the DELTA evaluation study, such sessions cannot be attended weekly. Instead, they specifically asked for a one-day workshop to be held. Based on material for the parental education sessions a preliminary version for this workshop has been conceived, but it still requires modification based on personnel feedback.

Tackling tobacco smoking

Regarding the main intervention effect, i.e., reductions of use for most substances including alcohol and methamphetamine, nicotine use was an exception as it did not decrease during the follow-up period (15). As the only substance, nicotine use is partly accepted by the institutional house rules, and adolescents are permitted to smoke outside. Smoking tobacco to obtain nicotine is the most prevalent use form among our sample, with 88% of them reporting to have used tobacco in the past year on an average of 26.5 days per month (5). Tobacco use in adolescents often already starts in early adolescence (5), and lingers on although tobacco is not allowed to be purchased for persons younger than 18 years. Not only is smoking tobacco associated with detrimental consequences to health and quality of life (20), it is also regarded as a risk factor for relapse in adolescents who have reached abstinence from illicit substance use (21). Therefore, a revised DELTA manual should also focus on smoking tobacco by providing guideline-oriented aids (22).

Study objectives/aims

In the publicly funded study DELTA-JU study (abbreviation of the German study title "DELTA in Jugendwohneinrichtungen"), we will aim: (A) to adjust sessions to the youth welfare institution setting and to needs of institutional personnel; (B) to evaluate whether the revised DELTA-JU manual is rated as acceptable by adolescent participants and institutional personnel; (C) to compliment previous results on DELTA effects, i.e., show that DELTA-JU is associated with reduced substance use (including tobacco use) and reduced SUD problems at FU.

Methods and analysis

Study design

Depending on their assigned condition, participants will be part of the trial for 17 or 33 weeks in total, see Table 1 for the SPIRIT schedule of enrollment, interventions, and assessments (Figure 1).

To achieve the outlined aims, we conceptualized an explanatory three-stage study over the course of 24 months, see Figure 2 for the 24-month study schedule. After adjusting the DELTA manual (12), to feedback from youth welfare institution personnel (content analysis of semi-structured qualitative interviews) in the adjustment stage, participants are cluster-randomized (institution as cluster, allocation

TABLE 1 SPIRIT Schedule of enrolment, interventions, and assessments.

TIMEPOINT	Study period					
	Enrollment	Allocation	Post-allocation	FU (immediate condition) BL (WL condition)	Post-allocation	FU (WL condition only)
	Week 0	Week 0	Week 1–16	Week 17	Week 17–32	Week 33
Enrolment						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions						
DELTA-JU, immediate condition			◆———			
DELTA-JU, WL condition					———◆	
Assessments						
Evaluation of intervention			X	X	X	X
Substance use and SUD	X			X		X
Co-occurring psychiatric problems	X			X		X
Risk factors for substance use and SUDs	X			X		X
Cognitive functioning	X			X		X
Biological markers	X			X		X

BL, baseline; FU, follow up; SUD, substance use disorders; and WL, waitlist control.

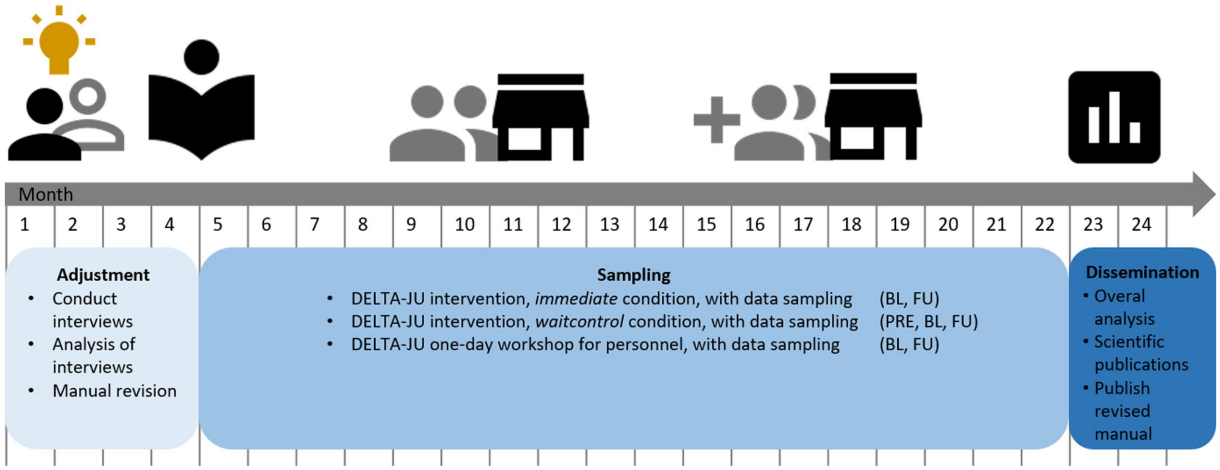

FIGURE 1
Overall study schedule and timeline.

by unblinded principal investigator who assigns the group consecutively to the sequence "intervention-waitlist-intervention-waitlist") to either one of two study arms [immediate treatment condition vs. waiting list control group condition (WL) with SUD treatment after 16 weeks] during the sampling stage. In terms of the Medical Research Council Framework for the evaluation of complex interventions (23), this design can be considered a pragmatic trial in "phase 2," which implies that theoretically relevant aspects have been previously identified (pre-clinical research, phase 0) (12), and that components of interventional procedures are readily available (modeling research, phase 1) (12). Further elements of a pragmatic trial are a simplified analysis design and uncontrolled environments (24). Blinding of participants, care providers, outcome assessors, or analysis is not feasible in this trial. In sum, the chosen design significantly differs in several relevant aspects from 'classical' cluster-randomized RCT (phase 3).

Also during the sampling stage, youth welfare institution personnel receives a newly designed one-day workshop on SUD-relevant topics. After completion of data sampling from adolescent DELTA-JU participants and personnel who evaluate the workshop, the dissemination stage starts where the DELTA-JU manual and overall evaluation results on the resulted DELTA-JU intervention are published. All measures and procedures are approved by ethics committee of the Technische Universität Dresden as an amendment to the DELTA evaluation study (approval in Jan 2022, number: EK 66022018).

Adjustment stage

During the adjustment stage in months 1–4, youth welfare institutions focusing on full-time housing for adolescents with SUDs are identified by contacting communal youth service authorities that typically provide long-term accommodation, in-house schooling, and psychosocial support for abstinent adolescents with SUDs. Identified institutions will receive letters or emails where study aims, procedures, and conditions are explained, asking for a collaboration. A formal cooperation agreement will be obtained with them. Institutional personnel will ask all adolescents and their legal guardians about their interest to participate, and will help to disseminate study information material. Furthermore, institutional personnel will be asked to participate in individual interviews (n = 10). The audio-taped interviews will take place in a separate room on an individual location to provide privacy. Interviews follow an semi-structured guideline in accordance with standards in the field of qualitative methods (25–29), with questions about the following areas of interest: (1) what are organizational challenges to implementing weekly group session in the institution (e.g., already existing therapeutic offers), (2) what session would be necessary and what problems do adolescents encounter in the institution, and (3) which needs does the personnel have regarding the one-day workshop? Responses will be analyzed with content analysis (29, 30) and/or Grounded Theory (29, 31). Thereby identified aspects in each of the three areas will be discussed by the study team so that for each aspect, at least one way how to implement it into the revision of DELTA is defined and subsequently carried out. Additionally, expert knowledge of the principal investigators will help to revise content and procedures of the manual in order to optimize its fit for the youth welfare institutional setting. The adjustment stage ends with the finally revised DELTA-JU manual including revised materials for adolescents as well as for personnel regarding the one-day workshop.

Sampling stage

During the sampling stage in months 5–22, adolescents will be recruited in cooperating youth welfare institutions in the study region, followed by a group-wise cluster-randomization. Adolescent participants will be prospectively assessed both at baseline (BL, a week before the intervention starts) and at follow-up (FU, 16 weeks after first group session). Those in the WL group will receive an additional pre-assessment (PRE, 16 weeks before intervention starts) for the WL to control for natural development. Assessments will take place in the youth welfare institution if possible, or in our outpatient clinic, e.g., for physical examinations. Questionnaires will be filled out in participant's free time. Participants will be reimbursed at PRE (15 EUR), BL (20 EUR), and FU (40 EUR). The DELTA-JU group and individual sessions will be carried out as outlined below ("Interventions") with possible changes due to the revision process. Study team members (i.e., psychologists, medical doctors, doctoral students, and student assistants from psychology, medicine, social work, or similar) who conduct the sessions or any assessment will be trained and supervised by the principal investigators.

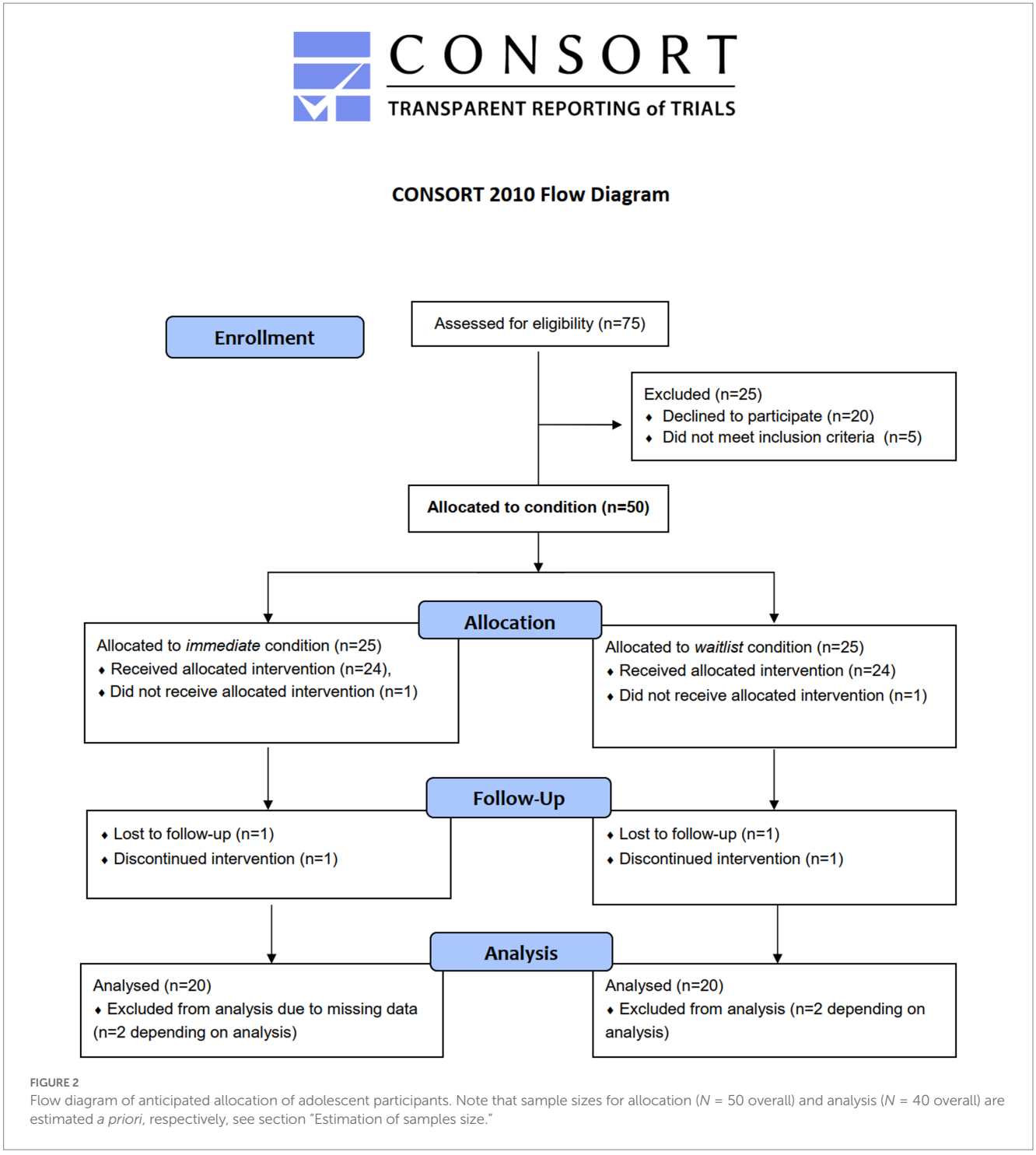

FIGURE 2
Flow diagram of anticipated allocation of adolescent participants. Note that sample sizes for allocation (*N* = 50 overall) and analysis (*N* = 40 overall) are estimated *a priori*, respectively, see section "Estimation of samples size."

During the same time, personnel from the youth welfare institutions will receive the revised one-day workshop on SUD-relevant topics. Workshops will be carried out either in the institutions themselves, in our outpatient clinic, in a public place, or via video conference if necessary due to restrictions for the prevention of COVID-19 infections. Whenever possible, personnel from similar institutions will be allowed to participate in the workshop. Personnel will also be assessed twice (BL at beginning and end of the workshop day, FU 16 weeks later) with questionnaires regarding the evaluation of workshop content and organization. All procedures were conducted in accordance with the Declaration of Helsinki, publicly pre-registered and approved by the local Institutional Review Board (see "Ethics" section below). For details on the dissemination stage, see "Dissemination" section below. The treatment and measurement schedule is shown in Figure 3.

Setting and participants

Youth welfare institutions will be approached if they are in the study region (district of Saxony and, if feasible, surrounding areas in Brandenburg and Thuringia). Generally, those institutions

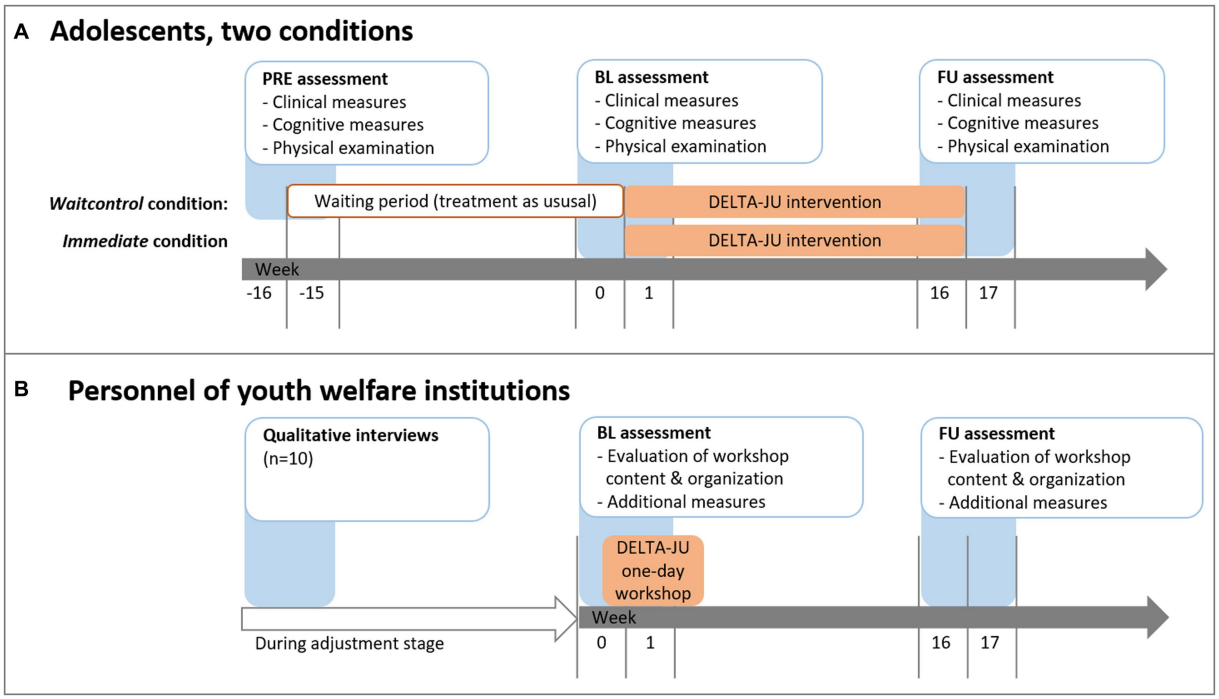

FIGURE 3
Treatment and measurement schedule for (a) adolescents and (b) youth welfare institution personnel. Timing of the 1-day workshop may vary for each institution based on time constraints of the personnel.

specialized in SUD care are placed outside of metropolitan areas (32) in order to reduce risk factors for relapse (such as contact to drug dealers) (33). Adolescents and their legal guardians will be approached by personnel of participating institutions. If interested, study personnel will hand out information material and will answer all questions in person, via telephone or via e-mail. Consent will be given after additional verbal information to adolescents. Inclusion criteria for adolescents are: (1) aged 12.00–17.99 years, (2) SUD diagnosis, or (3) chronic substance use during the past. The only exclusion criterion is low cognitive functioning (intelligence quotient <70). For BL-FU analyses, we will not analyze participants who did not attend any of the 16 sessions for whatever reason or if study participation was discontinued due to an adverse event. Participants choosing to discontinue are immediately asked whether they want to provide data on primary outcomes anyhow. Personnel of youth welfare institutions is included if they work with at least 20 h/week in a cooperating institution. The anticipated flow of adolescent participants is shown in Figure 2. At the time of writing this protocol, study registration is completed (01. Feb 2022) and the first adolescent participants are being recruited, randomized, and enrolled (starting 02. Feb 2022).

Interventions

DELTA intervention before revision

The manualized DELTA intervention (12) aims to reduce substance use and SUD-related problems to obtain abstinence and general well-being. It combines motivational interviewing, contingency management, cognitive-behavioral, and systemic therapy, see Table 2. Weekly group sessions of 60-min with 3–8 adolescents are led by up to two psychologists, who also conduct up to eight individualized 1-on-1 sessions (30 min) for each participant. Group sessions follow a structured plan including recurring elements (past-week craving review, checking homework, setting session goals, session-specific content, getting new homework, mindfulness exercise or reflection and feedback, and sporadic urine testing) and session-specific work sheets, but it also includes role plays, presentations, white-board actions, written self-evaluations, experimentation with skills boxes, mindfulness exercises etc. Attendance of all sessions is required and formally accepted within a signed "therapy contract." Exemptions from sessions need an *a-priori* explanation (e.g., doctor's appointment). When two or more meetings were missed without a valid explanation, or a sporadic drug urine test was positive on two occasions, adolescents have to be temporally excluded from group sessions for 8 weeks. Re-entry into the group sessions was possible after 8 weeks or a consultation with the attending therapist.

Waiting list control group

Participants whose group was cluster-randomized to the WL condition are not offered group sessions until 16 weeks have passed. During this period, adolescents may seek any kind of treatment as usual, including medication for co-occurring disorders or any kind of SUD treatment. Afterwards, DELTA-JU is provided in the same way as in the immediate treatment condition described above. The pre-treatment waiting period acts as a naturalistic comparator to the treatment. It is a suitable comparator given that many of the possible confounders (housing, timespan since previous

TABLE 2 Intervention content of the DELTA intervention before revision.

Session	Topic	Goal(s)
Adolescent patients group		
1.	Use and motivation to stop	Link substance use to SUDs Discover personal abstinence motivation
2.	Triggers	Identify triggers for craving and relapse
3.	Skills	Explore anti-craving skills
4.	New challenges	Develop situational anti-relapse strategies
5.	Relapse and stress	Reduce stress to prevent relapses
6.	Self-esteem	Develop self-esteem
7.	Honesty	Develop honesty in substance use self-reports
8.	Depression	Prevent and cope with depressiveness
9.	Boredom	Prevent and cope with boredom
10.	Understanding emotions	Identify emotions and associated reactions
11.	Coping with emotions	Promote activities to evoke positive emotions Avoid activities/situations associated with negative emotions
12.	Relapse justifications	Avoid situations with relapse risk
13.	Anti-relapse training	Revisit relapse prevention strategies, especially "3. Skills"
14.	Setting personal limits	Respect needs and limits of self and others learn to say "yes" and "no" if adequate
15.	Alcohol	Understand alcohol as a risky drug
16.	Review (*or optional:* shifting addictions)	Evaluate own progress understand that excessive use of other substances or media or internet puts oneself at risk for future disorders
Parental education group		
1.	SUDs[a]	Understand SUD development
2.	Substances[a]	Understand effects of different psychoactive substances
3.	Recovering families[a]	Understand SUD treatment stages
4.	Relapse[b]	Accept relapse as possible part of recovery Develop strategies when relapse occurs
5.	Living with addiction[b]	Reflect child–parent relationship reflect own parental style
6.	Communication[b]	Reflect own communication behavior Develop alternative strategies for problematic communications
7.	Nonviolent communication[b]	Develop and train basic principles of nonviolent communication
8.	Self-care[b,c]	Understand necessity to take care of oneself Reflect on other family members/siblings

SUD, substance use disorders. [a]based on a digital presentation; [b]based on work sheets and material for multi-parent exchange; and [c]an optional ninth session with individual topics may be offered.

detoxification treatment, availability of concurrent treatments/medication, psychosocial support, schooling situation etc.) should be equally present or absent in both conditions. Since concomitant treatments are allowed and documented in both conditions, we will be able to control for this confounder while at the same time providing a comparator group that represents the heterogeneity of SUD care in this population.

One-day workshop for personnel

The workshop will be based on content both from the parental education group (see Table 2) and previous presentations held for personnel of county administrations, medical students, police officers, teachers, and educators. If applicable, we may use computerized presentations, videos, worksheets, role play instructions, case vignettes, panel discussions etc. as educational methods.

Quantitative measurements

Primary outcomes in terms of study aims for adolescents are SUD-related subjective utility (GEJ), substance-related craving as a measure of relapse risk (MaCS), SUD severity (AUDIT, DUDIT, and FTND), and self-reported past-month tobacco use (substance use interview). For personnel, primary outcomes are SUD-related subjective utility and satisfaction ratings concerning the workshop organization (GEB-K, GEB-S). Secondary outcomes for adolescent participants are similar to those from the DELTA evaluation study (15) and include psychopathologies (BDI-II, PQ-16, UCLA-PTSD, and YSR), life satisfaction (SWLS), and perceived stress (ERI-S-10, PSS-10). For sample characterization, check of inclusion criteria, and for exploratory analysis in combination with data from that study, we will also apply additional measures that are either clinical standard

in our outpatient clinic (e.g., tests of intelligence or cognitive performances) or that are of research interest yet not related to the main study aims (e.g., analysis of epigenetics in blood, cortisol in saliva and hair). Table 3 lists all quantitative measures which are applied in the DELTA-JU study to obtain outcomes. Measures related to study hypotheses (AUDIT, DUDIT, FTND, MaCS, GEJ, GEB, and substance use interview), exploratory hypotheses (BDI-II, ERI-S-10, PQ-16, PSS-10, SWLS, UCLA-PTSD, and YSR), study inclusion (MINI-KID, C-DIPS) as well as measures which were generated (GEJ, GEB) or adapted (MQ-RS, CO in breath, physical examination) for this study are presented in more detail with references to their German versions. It should be noted that items from several instruments had to be reworded so that the formal German addressing of participants ("Sie," "Ihr") is replaced with the informal German addressing ("Du," "Dein") that is more adequate when addressing children and adolescents. Details for other instruments and procedures can be found in the referenced sources.

Severity of SUDs

Severity of SUDs is measured via three total scores of self-report instruments assessing substance use parameters as well as related problems. The Fagerström Test for Nicotine Dependence (FTND) (22) has six items with 2–4 answer options per item, resulting in a total score of 0–10 points with higher points indicating stronger problems due to tobacco use in the past week. The Alcohol Use Disorders Identification Test (AUDIT) (36) has 10 items with 3–5 answer options resulting in a total score of 0–40 points for alcohol-related problems in the past 12 months. The Drug Use Disorders Identification Test (DUDIT) (37) has 11 items with 3–5 answer options, resulting in a total score of 0–44 points for drug problems in the past 12 months.

Craving

The Mannheimer Craving Scale (MaCS) (38) is a self-report questionnaire with 12 items, assessing substance-related urges to consume psychoactive substances/drugs. Items are based on a five-point scale with item-specific verbatim for each point, e.g., item 11: "How strong is your urge to take the substance? 0 = I feel no urge, 1 = I feel some urge, 2 = I feel a strong urge, 3 = I feel a very strong urge, 4 = The urge is absolutely overwhelming and cannot be influenced."

Substance use

Substance use is assessed via structured interview (5) by a clinical psychologist who asks for the number of use days and the amount per use day on average for each of the following substances both for past month and past year: nicotine, alcohol, cannabis, methylenedioxymethamphetamine (MDMA), amphetamine, methamphetamine, hallucinogens, opiates, inhalants, or other. These quantity and frequency reports are multiplied to obtain a quantity-frequency index (e.g., for alcohol: 10 drinking days past month × 4 standard drinks per drinking occasion = 40 consumption units per month during the past year). Additionally at BL, the interviewer will ask the same questions for past year-use as well as for age at first use per substance. Changes in the past-month quantity-frequency index for tobacco use will be a primary outcome. Other substances are only explored given that youth welfare institutions do not permit any other substance use than smoking.

Subjective utility

For adolescents, a self-designed questionnaire ("Gruppenevalution Jugendliche," GEJ) from the DELTA evaluation study (15) will be used. The questionnaire contains 20 items that are related to SUD-specific subjective utility as trained in the group sessions (e.g., "I recognize my triggers," "I've learned to deal with boredom," "I have more control over my SUD," and "I have more drug knowledge"). Items are rated on a five-point Likert scale (0 = does not apply at all, 1 = applies a bit, 2 = applies rather than not, 3 = applies most of the time, and 4 = applies always) to indicate how much participants approve each statement.

For personnel, a comparable self-designed questionnaire ("Gruppenevalution Betreuer," GEB) was designed. One part asks for changes in subjective utility (GEB-K) induced by the one-day workshop, e.g., "I feel that I have learned new skills for coping with the child," "I feel less alone with the substance use problems of the child," "I feel I have gained more control over the current substance use problems of the child." Personnel is instructed to rate it is approval for each of the 14 GEB-K statements using the same five-point Likert scale as the GEJ. The second part asks for the satisfaction (GEB-S) with the workshop, separately for organizational aspects (eight items, five-point Likert-scale from 1 = does not apply at all to 5 = absolutely applies, e.g., "The trainer was well-prepared," "Material was well-designed and could be readily used") and for applicability of workshop content to their daily work (six items, five-point Likert-scale from 1 = not helpful at all to 5 = very helpful, e.g., "Comorbid disorders," "Stages of recovery"). GEB-K and GEB-S have been used during the piloting of the DELTA evaluation study (15).

Secondary outcomes

Depressiveness is assessed with the Beck Depression Inventory II (BDI-II) (39), a self-report questionnaire with 21 items (Likert scale ranging from 0 to 3) resulting in a sum score.

The Youth Self Report form (YSR) (58) covers a range of different psychopathologies via 118 items (Likert scale ranging from 0 to 2). We will analyze the subscales for depression-related affective symptoms ("YSR anxious/depressive"), social impairments ("YSR social withdrawal"), attention-deficit disorder-related problems ("YSR attention"), and conduct disorder-related problems ("YSR aggressive" as well as "YSR dissocial").

Psychopathologies related to post-trauma and post-traumatic stress (PTSD) are assessed via the UCLA PTSD scale (59) that assesses all DSM-5 PTSD symptoms related to the three scales "intrusion," "avoidance," and "hyperarousal" (scored here as present or absent).

Psychopathologies related to prodromal symptoms of psychoticism are assessed via the 16-item Prodromal Questionnaire (PQ-16) (60), where binary-rated items are summed up to a score.

Current life satisfaction is rated by adolescents on the Satisfaction with Life Scale, German version (SWLS) (41), a five-item questionnaire. The SWLS covers global life satisfaction in contrast to related constructs such as positive affect or loneliness by asking for life conditions, achievements etc. to be rated on a seven-point Likert scale (1 strongly disagree to 7 strongly agree). Sum scores may range from 7 to 49, with higher scores indicating higher life satisfaction.

Perceived past-month stress in adolescents is assessed using the Perceived Stress Scale (PSS-10) (43) with 10 items rated on a five-point scale and resulting in a total sum score. Perceived current stress due

TABLE 3 Assessment instruments for adolescent participants as well as personnel of youth welfare institutions (highlighted with *).

Construct	Reference	Instrument used per assessment		
		PRE (week –16)	Baseline (week 0)	FU (week 16)
Domain: Evaluation of intervention				
Increase in subjective utility, skills	(15)	–	–	GEJ
Increase in subjective utility, skills	–			GEB-K*
Satisfaction with one-day workshop	–	–	–	GEB-S *
Satisfaction with DELTA-JU group session (after each session)	(34)	–	GTS-P	–
Satisfaction with DELTA-JU group session (after each session)	(34)	–	GTS-T[a]	–
Domain: Substance use and SUD				
Substance use (generic interview)	(5)	interview	interview	interview
Diagnosis of SUD, co-occurring mental disorders	(35, 61, 62)	C-DIPS/ MINI-KID	C-DIPS/ MINI-KID	C-DIPS/ MINI-KID
Severity of SUD: Alcohol use disorder	(36)	AUDIT	AUDIT	AUDIT
Severity of SUD: SUDs for illicit substances	(37)	DUDIT	DUDIT	DUDIT
Severity of SUD: Tobacco use disorder	(22)	FTND	FTND	FTND
Craving for substance use	(38)	MaCS	MaCS	MaCS
Domain: Co-occurring psychiatric problems				
Depressiveness	(39)	BDI-II	BDI-II	BDI-II
Psychotic symptoms	(40)	PQ-16	PQ-16	PQ-16
Psychopathologies	(58)	YSR	YSR	YSR
Satisfaction with life	(41)	SWLS	SWLS	SWLS
Traumatic events and post-traumatic problems	(42)	UCLA PTSD	UCLA PTSD	UCLA PTSD
Perceived stress	(43)	PSS-10	PSS-10	PSS-10
Perceived stress	(44)	–	ERI-S 10*	ERI-S 10*
Domain: Risk factors for substance use and SUDs				
Tobacco use: motives	(45) [c]	MQ-RS	MQ-RS	MQ-RS
Tobacco use: expectancies	(46) [c]	SEQ	SEQ	SEQ
Tobacco abstinence: self-efficacy	(47)	SER	SER	SER
Tobacco abstinence: percentage of smoking peers	(48)	PSP	PSP	PSP
Temperament	(49)	SURPS	SURPS	SURPS
Sociodemographics (generic questionnaire)	(5)	–	Generic [b]	–
	–	–	Generic*	–
Domain: Cognitive functioning				
Memory	(50)	VLMT	VLMT	VLMT
Alertness, divided attention, inhibition/impulsivity	(51)	TAP	TAP	TAP
General executive functioning	(52)	Stroop	Stroop	Stroop
	(52)	Stop-signal	Stop-signal	Stop-signal
Intelligence	(53, 54)	–	WISC-V / WAIS-IV [d]	–
Domain: Biological markers of substance use and stress				
Carbon monoxide in exhaled breath	(22)	CO in air	CO in air	CO in air
Genome wide DNA methylation	(55)	Blood	Blood	Blood
Cortisol Cortisol	(56) (56)	Saliva Hair	Saliva Hair	Saliva Hair
Weight, height, acute physical diseases	–	examination	examination	examination
Pubertal development (questionnaire)	(57)	PDS	PDS	PDS

* self-report of personnel. [a] group of adolescents is rated by the therapist. [b] individual adolescent is rated by legal guardian. [c] translated or adapted for this study. [d] WISC until age 16, WAIS for older adolescents.

to occupational demands are assessed via the 10-item Effort-Reward Imbalance at work scale short form (ERI-S-10) (44) with Likert-scaled items (range 1–4) and a total sum score.

Additional measures

Current DSM-5 diagnoses for SUDs as well as co-occurring mental disorders are assessed with the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (35) or the Childrens' Diagnostic Interview for Mental Disorders (C-DIPS) (61, 62) depending on license availability. Both instruments are structured interviews for DSM-5 disorders in children and adolescents with substantial to almost perfect interrater and test–retest reliability (35, 61).

Sociodemographic characteristics of adolescents are acquired via questionnaire from legal guardians, including information on participant's age (in years), gender, parental school education (list of school graduation options), and relationship status of biological parents. Sociodemographic characteristics of personnel is obtained via standardized questions regarding age (in years), gender, school education (list of school graduation options), and current SUD-related subjective utility (percentage, from 0 = 'none at all' to 100 = 'all you must know').

Adherence to therapy is operationalized through the number of sessions attended by each adolescent (ranging from 1 to 16 sessions, with more sessions indicating stronger adherence) and by subjective rating of active participation by each adolescent itself (five-item questionnaire, GTS-P) (34). Although participants are instructed to attend to all 16 weekly sessions as well as individual sessions, thus only participants with one or more attended sessions will be analyzed. The study team member who conducts a group session will additionally rate how well the group participated actively in each respective session, and whether any adverse events occurred (nine-item questionnaire, GTS-T) (34). Drop-out from the study as well as discharge of adolescents from an institution will be recorded by study personnel.

Substance use motives specifically for smoking are assessed via the Motives Questionnaire Revised for Smoking (MQ-RS), an instrument we developed. The MQ-RS uses the 20 items and the five-point scale [ranging from 1 = (almost) never to 5 = (almost) always] from the established drinking motives measure of Cooper in its revised form (45). In contrast to drinking motive measure, we had to reword items 8 ("…about not smoking" instead of "…about not drinking") and 10 ("…to feel the kick" instead of "…to get high") in order to avoid alcohol-specific or smoking-unrelated wording.

Using a breath analyzing device, we will measure the amount of carbon monoxide (CO) in breath in accordance to standards in the field (63), with CO ≤ 20 ppm indicating point abstinence from tobacco smoking (22).

The physical examination is carried out by medical students who is supervised by a principal investigator. Participants are measured (height in cm, weight in kg) and examined according to clinical routines. Any deviations from normal physical development are noted in a protocol, e.g., visible wounds, signs of diseases, or basic neurological problems. Adolescents will be asked for current infections, diseases, and medications. In case of psychoactive medication or acute infectious diseases, saliva and blood will not be collected or analyzed, as these factors a confounding issues.

Data management

Data quality is checked biannually via interim analysis and auditing by the principal investigators regarding outliers, subgroup means, and missing data patterns of primary and secondary outcome data, with the final decision to terminate the trial if applicable. As in the previous DELTA evaluation study, missing item values will be replaced by the mean of questionnaire items, if 80% or more of the items were answered (15). Items that may not be replaceable have been anticipated to appear in approx. 10% of the cases. The sample size estimation accounts for this by loss, see Figure 2.

Data analysis

Analyses will be conducted with the most recent version of the software "IBM SPSS Statistics," currently version 27.0. Adolescents are analyzed as randomized if they participated in at least one DELTA session (DELTA condition only). To test all non-descriptive hypotheses (see below, hypotheses 2–4), a repeated measures MANOVA will be conducted using time as factor ("within factor") given the explanatory nature of the trial and the non-importance of between-group effects. A significant reduction over time (BL vs. FU) in all $N = 40$ participants across all metric outcomes (MaCS score, FTND score, DUDIT score, AUDIT score, and cigarettes per day during the past month according to substance use interview) indicates a relevant intervention effect. This multivariate approach will limit the chance for false-positive results as otherwise possible due to multiple testing. Effect sizes will be classified into small effects ($\eta^2 \geq 0.01$), medium effects ($\eta^2 \geq 0.06$), and large effects ($\eta^2 \geq 0.14$). In case of severe non-normality of outcome variables, we will have to apply non-parametric tests instead of the repeated measures MANOVA.

Hypotheses

Aim (A) is reached when for each need, identified through qualitative analyses of interviews, one or more adjustments to the content or procedure of DELTA-JU is documented. No quantitative hypothesis is applicable. Aims (B) and (C) are achieved through testing the following hypotheses in adolescents who are abstinent for alcohol and drugs except nicotine/tobacco:

1. Adolescents: relevant increase in SUD-related subjective utility through FU (descriptive: a medium rating of 2.0 or higher in the respective GEJ items across participants);
2. Adolescents: significant reduction of substance-related craving as a measure of relapse risk ($p < 0.05$, MaCS score) through FU;
3. Adolescents: significant reduction of SUD severity ($p < 0.05$, scores of FTND, AUDIT, and DUDIT) through FU;
4. Adolescents: significant reduction of self-reported past-month tobacco use through FU ($p < 0.05$, substance use interview);
5. Personnel: relevant increase in SUD-related subjective utility through FU (descriptive: a medium rating of 2.0 or higher in the respective GEB items across participating personnel); and
6. Personnel: high satisfaction ratings concerning the workshop organization (descriptive: a medium rating of 4.0 or higher in the respective GEB items across participating personnel).

Additionally, secondary outcomes in adolescents (BDI-II, PQ-16, UCLA-PTSD, PSS-10, and SWLS) and personnel (ERI-S-10) will be tested exploratorily for changes through FU as previously done in the DELTA evaluation (15). All reductions through FU in adolescents are expected to be descriptively larger than reductions over the natural course, i.e., from PRE to BL in the WL group.

Estimation of sample size

Sample size will be optimized to achieve sufficient power for hypothesis testing. Assuming an error probability of $\alpha = 0.05$, test power of $1-\beta = 0.95$, a large effect of time with $f = 0.40$, and a repeated measures correlation of $r = 0.1$, we computed minimum sample sizes of $N = 40$ analyzed adolescents and $N = 40$ analyzed personnel with the G*Power software (64). Large effect sizes were anticipated given that the actual intervention effect size (15) had not yet been analyzed at the time of the inception of DELTA-JU and the proposal for funding and ethics approval in 2020.

Considering the dropout rates from BL to FU for adolescents (assuming 20%) and personnel (assuming 10%), at least $N = 50$ adolescents and $N = 45$ personnel will have to be included at BL. In case that dropout rates exceed 20%, we will continue to sample participants in order to achieve the required analysis sample size of $N = 40$ nonetheless as long as study funding is available. For qualitative interviews, a sample size of $N = 10$ was deemed as an adequate compromise between resources and expected output.

Discussion

The DELTA-JU study will create a setting-specific manual for highly vulnerable adolescents who suffer from one or more SUDs, and, in many cases, from co-occurring mental disorders. We believe that DELTA-JU will be (a) properly adjusted to setting-specific needs of youth welfare institutions offering housing for adolescents with SUD, (b) accepted both by adolescents and the institutions' personnel, and (c) effective in remaining abstinent from substances, reducing tobacco smoking, and reducing SUD problems. Providing feasible and effective treatments that are accepted by their respective target population is one primary goal set both for mental health research and practice in Europe (65).

As in all interventions, an age-specific approach is warranted when approaching children and adolescents. DELTA and DELTA-JU indeed provide an age-adequate intervention that includes material, methods, and content created for adolescents' needs specifically while avoiding topics and approaches better suited for adults or older adults, e.g. (66). Furthermore, DELTA and DELTA-JU integrate modules on prevalent and outcome-relevant problems besides SUD, i.e., for depressiveness, for emotion regulation, and coping with stress and boredom. Addressing such co-occurring psychopathologies is in line with current recommendations for state-of-the art psychotherapeutic treatments (67). In the future, psychotherapeutic interventions such as DELTA-JU may be accompanied by including virtual reality elements or mobile phone-based elements.

Giving that effects can be independently replicated, it can be disseminated within other institutions of youth welfare. This will help institutions to professionalize their service for adolescents with SUD and it provides another currently lacking tool (68) for the outpatient treatment of SUDs before and after inpatient detoxification treatment (69). At the same time, we believe that besides treatment for diagnosed SUDs, efforts in prevention and early intervention are necessary nonetheless (70).

From a long-term perspective, programs such as DELTA-JU may help to alleviate the immense societal costs relating to consequences of alcohol use (27pprox. 32.5 billion EUR per year in Germany) (71), tobacco use (97.2 billion EUR) (72), cannabis use (0.9 billion EUR) (73), and the use of further substances for which no estimations are available.

Strengths and limitations

The presented study design has several strengths. First, it is in line with ethical requirements that all adolescents are offered treatment. Waiting for 16 weeks in the WL condition still seems adequate given that adolescents may reside for up to 2 years in youth welfare institutions. In randomized clinical trials, for example, only cases may have received treatments. Second, it requires a smaller sample when participants become part of several analysis groups (intervention vs. WL). Third, alternative explanations of time effects may be controlled for by comparing BL-FU effects with PRE-BL effects.

Challenges arise from uncontrolled parallel treatments during the waiting period. Such treatments cannot be included in the quantitative estimation of treatment effects due to the limited number of participants in each group. Furthermore, homogeneity of cooperating youth welfare institutions is limited. Results may thus have to be replicated in other and diverging institutions. Although the sample size was *a-priori* calculated to maximize the use of available resources, drop-out rates may be unexpectedly high. In this case, additional participants and institutions may have to be recruited. In case of limited sample size, using Bayesan methods instead of testing for differences from zero may be advisable (74). Both the AUDIT and DUDIT have been previously used to assess changes in alcohol- and drug-related problems in adolescents and young adults using 3-month intervals between BL and FU (75, 76). Nevertheless, it remains possible that small changes in problems might go unnoticed given that both instruments cover 12 month periods. Another limitation arising from the limited sample size in a phase II study is the impossibility to adjust for several baseline variables. Such superior analysis strategies are not feasible at this point of the intervention development but will be imperative during phases III/RCT and phase IV studies in the future. The same holds true for the analysis of relevant patient subgroups (e.g., differentiating those with primarily alcohol-related problems from those with primarily cannabis-related problems) and intention-to-treat analyses or sensitivity analysis. Finally, additional measures that would objectify relapse to the use of alcohol or other drugs were not funded and will have to be implemented in a future trial, preferably a multi-center RCT testing DELTA-JU against treatment-as-usual.

Conclusion

By developing the existing DELTA manual further in terms of setting-specific adaptions (DELTA-JU) for vulnerable adolescents suffering from SUDs, we may add another treatment option for this at-risk population. This requires evidence for acceptability, feasibility, and effectiveness as far as this exploratory trial is able to produce them. We hope that DELTA-JU can finally be disseminated within other institutions of youth welfare to help these adolescents to remain abstinent from alcohol and other drugs in the future.

Ethics statement

This trial and all its procedures are in accordance with the Declaration of Helsinki. It has been submitted as an amendment to the DELTA evaluation study to the ethics committee of the University Hospital C. G. Carus Dresden and Technische Universität Dresden (approval in Jan 2022, number: EK 66022018 including amendments). It was furthermore pre-registered at the German Clinical Trials Register (DRKS, reference number: DRKS00027913, see www.drks.de/DRKS00027913), official as of 01.Feb 2022) where important protocol modifications will be communicated, see also SPIRIT 2013 checklist [75] (Supplementary information 1) and World Health Organization Trial Registration Data Set (Supplementary information 2) for details. An English version will be automatically uploaded to http://apps.who.int/trialsearch/. Both adolescent participants and personnel will have to consent to participate. In the case of adolescents aged 17 or younger, legal guardians as well have to agree to study participation by written consent after a comprehensive written and/or verbal information. Similar written information will be handed out to all participants, including information on study aims, procedures, duration, data security, voluntariness of participation and the right to leave the study at all times. Importantly, participants will be informed that any information on potentially illegal actions such as purchase, possession, sale, or use of illicit substances will not be forwarded to legal authorities, legal guardians or youth welfare institution personnel in accordance with data protection laws. Anonymity of study data will be assured by saving all information under an individual arbitrary ID code, with the linkage file between ID code and name only available to study personnel. All personnel including student assistants and master/doctoral candidates will undergo trainings on data security measures and good scientific practice as supervised by the principal investigators and/or the sponsoring institution. Study data will be hosted on servers of the funding institution (Technische Universität Dresden) in accordance with local data security laws. We do not seek to publish any identifying images or other personal or clinical details of adolescent participants that compromise anonymity. As for qualitative interviews of youth welfare institution personnel, we plan to publish anonymized sentences. Personnel will be informed in advance during the comprehensive written and/or verbal information, and will have to give written consent that they agree.

Author contributions

SK-P conceived the study. SK-P, LB, VR, and YG contributed to the study design. LB contributed to the determination of the research directions for the DELTA manual. SK-P, VR, and YG are grant holders. YG is conducting the primary statistical analyses. SK-P conducted the additional analyses. YG will act as the leading principal investigator, responsible for preparation of protocol and revisions, preparation of study material and assessment procedures, recruitment of cooperating youth welfare institutions, randomization, data management, budget administration, supervision of study personnel, and conducting main analyses. YG will be part of the steering committee that also includes co-PIs SK-P and VR. This committee will meet regularly to support YG and to discuss issues regarding data monitoring, analyses, and publication of results with accordance to ICMJE guidelines for authorship eligibility (http://www.icmje.org/recommendations/). All authors contributed to the article and approved the submitted version.

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Conflict of interest

SK-P, LB, VR, and YG are authors of the DELTA treatment manual, thus they receive honoraria for the manual as published by from Hogrefe Publishing.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1025347/full#supplementary-material

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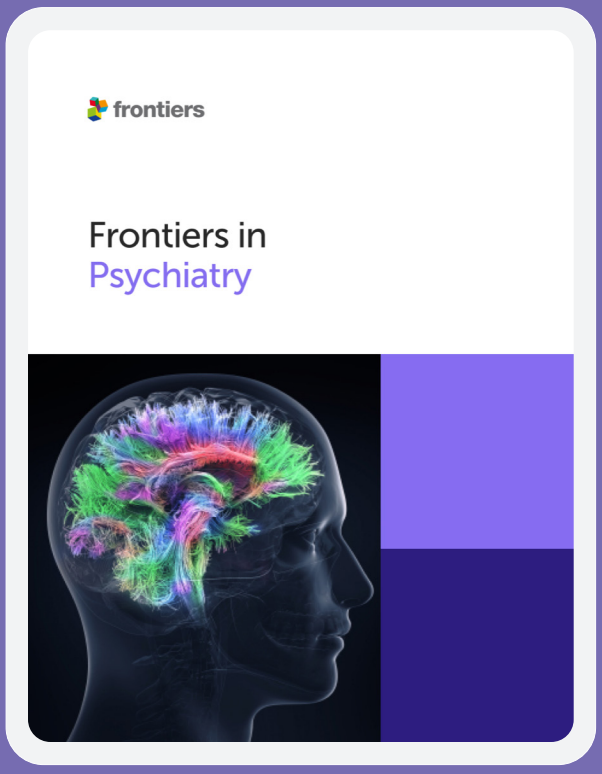

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