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Exploring prevention strategies and treatment in addictive disorders

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Exploring prevention strategies and treatment in addictive disorders

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Editorial: Exploring prevention strategies and treatment in addictive disorders

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vulnerability factors in addictive disorders, therapeutic approaches for addictive disorders, genetics and epigenetics of addictive disorders, pharmacological targets for addictive disorders, substance use disorders (SUD), cognitive-behavioral therapy and addictive disorders, gaming disorder (GD)

Editorial on the Research Topic
Exploring prevention strategies and treatment in addictive disorders

Addictive disorders are characterized as chronic illnesses that affect brain circuits related to reward, motivation, and memory. Dysfunctions in these circuits are associated with typical Substance Use Disorders (SUDs) features, such as the inability to abstain from seeking and using drugs, uncontrollable cravings, as well as impaired interpersonal relationships (1). Relapse is a key factor in SUDs, as a significant number of individuals who undergo treatment experience periods of relapse. This phenomenon underscores the chronic and complex nature of SUDs, where sustained abstinence is often challenging to achieve. Various factors contribute to relapse, including environmental triggers, stress, emotional instability, social pressure, and untreated mental health issues. These factors can interact and create a cycle wherein individuals struggle to maintain sobriety despite initial treatment efforts. Understanding the dynamics of relapse is crucial for developing effective interventions and support systems that address the multifaceted challenges of SUDs recovery. Despite extensive research on the neurocircuits implicated in addictive disorders over several decades, vulnerability factors and the neuronal, cellular, and molecular pathways underpinning these mechanisms remain inadequately understood (2).

In order to uncover new therapeutic approaches to obtain suitable treatments for SUDs, several strategies are being considered. The properties of pentilludin, a new and promising drug whose target is the receptor type protein tyrosine phosphatase D, are revised in this Research Topic (Uhl). The efficiency of the available pharmacotherapy to treat SUDs may vary from one abused drug to another. The study of Wang et al. revealed that buprenorphine, which is currently used to treat opioids and cocaine use disorders, could be a promising drug also for methamphetamine use disorder and relapse. Furthermore, the possible similarities between attention-deficit/hyperactivity disorder and SUDs have led van Ruitenbeek et al. to propose methylphenidate, which is indicated for attention-deficit hyperactivity disorder, as a potential effective drug as well for SUDs.

Besides pharmacological interventions, cognitive-behavioral therapy (CBT) has been proposed as an alternative approach for treating SUDs, together with pharmacotherapy or alone (3). In this Research Topic, it is reported the efficacy of a self-directed treatment workbook based on CBT and one motivational interview to promote changes in cannabis use in individuals who wish to recover with minimal professional support (Schluter et al.). Moreover, Hofsted et al. tested a 15-week CBT designed specifically for Gaming Disorder, that is recognized by the International Classification of Diseases under the section for addiction, and found statistically significant decreased symptoms, reduction in gaming hours and an increase in non-gaming leisure activities with reductions in depression and anxiety. On the other hand, parental monitoring has been proposed as a useful tool to protect adolescents against SUDs. In the study performed by Alexander et al. this hypothesis was examined and, through the twin design, genetic and environmental contributions to these relationships were measured. Although genetic influences on substance use and parental monitoring were detected, the data of this investigation point out to limited causal connection between parental monitoring and substance use in mid-to-late adolescent community samples.

The global rise in SUDs poses a significant health challenge driven by complex neurobiological mechanisms and exacerbated by lifestyle stressors. Understanding the molecular pathways and vulnerability factors underlying SUDs stages is essential for developing effective treatments. Thus, Mu et al., through a cross-sectional study, assessed the psychological factors and the history of methamphetamine use that could affect methamphetamine relapse. They found that individuals with methamphetamine use disorder informed of worse executive function and mental health. Their results also seem to indicate that the relapse rate might be influenced by the lower age of first methamphetamine use, while, specifically, repeated relapse could affect executive dysfunction.

Bioinformatics have become a crucial tool to elucidate different pathways involved in a same etiopathogenic origin. However, their results need to be examined in detail for a better interpretation. In this line, the role of the serine proteinase inhibitor A3 (SERPINA3), a differentially expressed gene identified by GEO2R tool, has been explored and identified as an important upregulated protein in alcohol use disorder, but it appears not usable as a predictive relapse marker (Zhang et al.).

Research has shown that microRNAs play a pivotal role in opioids abuse (4, 5). Concordantly, in this Topic Shi et al. report that the expression levels of miR-124 and its target protein IQGAP1 are linked with anxiety and depression symptoms, altering susceptibility and cognitive function in patients with morphine dependence.

Research efforts deal with a variety of abused substances as well as other addictive disorders, offering novel pharmacological targets and promising therapeutic approaches. However, further research is needed to establish evidence-based treatments, especially considering psychiatric comorbidities. Overall, the findings described in this Research Topic highlight the complexity of addictive disorders and the need for multifaceted approaches to its treatment and prevention.

Author contributions

SM-R: Supervision, Writing – review & editing. VG-M: Writing – original draft. FF-G: Writing – original draft. CN: Supervision, Writing – original draft, Writing – review & editing.

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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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ORIGINAL RESEARCH
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MiR-124 Regulates IQGAP1 and Participates in the Relationship Between Morphine Dependence Susceptibility and Cognition

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Background: Long-term excessive use of morphine leads to addictive diseases and affects cognitive function. Cognitive performance is associated with genetic characteristics.MiR-124 plays a critical regulatory role in neurogenesis, synaptic development, brain plasticity, and the use of addictive substances. As a scaffold protein, IQGAP1 affects learning and memory dose-dependent. However, the role of miR-124 and its target protein as potential addiction biomarkers and the impact on cognitive function have not been fully explored.

Method: A total of 40 patients with morphine dependence and 40 cases of healthy people were recruited. We collected basic and clinical information about the two groups. The Generalized Anxiety Disorder Scale (GAD-7), Patient Health Questionnaire-9(PHQ-9), Montreal Cognition Assessment Scale (MoCA), Pittsburgh Sleep Quality Index (PSQI) were used to assess the severity of depression, anxiety, depressive symptoms, cognitive dysfunction, and sleep quality.

Results: Compared to the control group, the morphine-dependent group had higher GAD-7, PHQ-9, PSQI scores, and more elevated miR-124 levels but lower MOCA scores and IQGAP1 levels. MiR-124, IQGAP1, the average intake last year were related to OASI scores.MiR-124, IQGAP1, PHQ-9 were associated with MOCA scores. In the multiple regression model, the levels of miR-124 and IQGAP1 were independent factors influencing the severity of morphine dependence. The level of miR-124 was an independent factor influencing the severity of cognitive impairment in patients with

morphine dependence. In addition, the luciferase report confirmed that IQGAP1 mRNA is the direct target of miR-124.

Conclusion: MiR-124 and its target protein IQGAP1 are involved in the regulation of addiction and cognitive function in patients with morphine dependence.

Keywords: morphine dependence, mir-124, IQGAP1, addictive, cognition

INTRODUCTION

Over the past two decades, the abuse of opioids has led to a high mortality rate (1, 2). Among opioid drugs, morphine is considered one of the most effective analgesics for application in postoperative and cancer pain, the trouble about overuse and addiction it causes is rather intractable. Morphine and other opioid drugs can induce a broad spectrum of pharmacological activity. Occurring in the central nervous system, this generates a series of symptoms like disturbances in mood and promotes anxiety, depression, and cognitive impairments (3, 4). Frequent exposure to opioids also causes deficits in learning, memory, attention, reasoning, and impulse control (5). More explanations about how morphine and other opioid drugs affect cognitive function must be clarified.

MicroRNAs (miRNAs) are small endogenous non-coding RNAs that negatively regulate protein translation by binding to the 3′-untranslated regions (UTRs) of their target messenger RNAs (mRNAs). Many pieces of evidence show that miRNAs play a vital role in various physiological and pathological processes such as neurological diseases, mental diseases, addictive diseases, and cognitive impairment. MiR-124 is one of the most conserved and expressed neuron-specific miRNAs (6). It is abundantly expressed in the hippocampus, and has significant activity in neurons that differentiate and affect the generation, survival, and neuron generation, branching, excitation, and plasticity of cells (7). In terms of substance abuse, studies have found that long-term and overuse of cocaine and amphetamine can cause changes in miR-124 levels (8, 9). IQ motif containing guanosine triphosphatase activating protein 1 (IQGAP1), is a new protein that supports long-term memory. It is a 190 kDa scaffold protein that contains multiple domains and can interact with different targets (10). As an essential component of NMDAR multiprotein complexes, IQGAP1 is involved in the N-cadherin/cytoskeletal IQGAP1/Erk signaling pathway. It contributes to GluN1/GluN2A trafficking and facilitates IQGAP1-influenced memory formation. In animal research, IQGAP1 knockout mice exhibited impairments in fear conditioning, significantly lower surface NR2A, and impaired ERK activity compared to their wild-type littermates. They also performed marked long-term memory deficits accompanied by an impaired hippocampal long-term potentiation (LTP) (11). In addition, miR-124 and IQGAP1 are co-expressed in neuronal cells, suggesting that IQGAP1 may be a direct target of miR-124 in the brain (12).

Based on previous studies, we hypothesized that IQGAP1, as a direct target of miR-124, may be involved in regulating the addiction and cognitive function of patients with morphine dependence. Therefore, the first aim of this experiment was to explore whether miR-124 and IQGAP1 are susceptibility markers of morphine dependence. The second aim was to investigate whether miR-124 and IQGAP1 affect cognitive function. The final aim was to determine whether IQGAP1 was the target of miR-124.

METHODS

Participants

From January 2021 to November 2021, 40 cases of morphine dependent patients (the morphine dependent group) were enrolled in Beijing Youan Hospital, Capital Medical University; 40 subjects of healthy people (the control group) were enrolled in Beijing Anding Hospital, Capital Medical University. Morphine dependent patients met the following criteria: (1) age of 18–45 years old; (2) diagnosis of Opioid Use Disorder Standard for DSM-5.The control group met the following criteria: (1) age of 18–45 years old; (2) there are no previous or current Axis I disorders, severe or unstable clinical diseases, neurological disorders, or any substance use 30 days before the study (self-report). Before all sample and data collection, participants were informed of the study's purpose and procedures, and signed an informed consent form. In addition, the Ethics Committee of Beijing Anding Hospital and Beijing Youan Hospital approved the trial.

Clinical Assessment

Opioid Addiction Severity Inventory (OASI) was used to assess the severity of morphine addiction in patients. It consists of 4 subscales: physical dependence, psychological dependence, health harm, and social functioning harm. Questions were asked about past month heroin use. Each item was scored using a 4-point Likert scale, and the severity of opioid dependence was assessed by summarizing the item scores (13).

The Generalized Anxiety Disorder Scale (GAD-7) was used to assess the degree of anxiety in patients. GAD-7 asks how often people have suffered from the seven core symptoms of GAD in the past 2 weeks, with response options of "not at all," "some days," "more than half the days," and "almost every day" (each option scored 0–3, total score 0–21). Researchers use GAD-7 as an indicator of treatment outcome in mixed anxiety and depression samples (14).

Patient Health Questionnaire-9(PHQ-9) was used to assess the severity of depressive symptoms. The PHQ-9 is a simple and validated self-rating scale for depressive disorders. It has good reliability and validity both as an aid in the diagnosis of depression and the assessment of symptom severity. The

scale consists of 10 items, including nine symptom scales and one total functional rating. It is a 4-level scale, rated by the frequency of symptoms in the last 2 weeks. The total score range was 0–27, with higher scores being more severe for depressive symptoms.

Montreal Cognition Assessment Scale (MoCA) was used to screen for cognitive dysfunction. The MOCA has 11 examination items, including eight cognitive domains. The total score is 30, and a score of $\geq$26 is considered normal cognitive function, plus one if the number of years of education is $\leq$12, with higher scores indicating better cognitive function. The scale is highly sensitive, contains critical cognitive domains, has a short test time, is suitable for clinical application, and is more acute in screening for mild cognitive impairment.

Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality. The PSQI was developed in 1989 by Dr. Buysse, a psychiatrist at the University of Pittsburgh, to assess sleep quality in the last month. The PSQI consists of 19 self-rated and five other-rated items. The 19th self-rated item and the 5th other-rated item are not involved in the scoring and consists of 7 components, each of which is scored of 0 to 3. The cumulative score for each component is the total PSQI score, which ranges from 0 to 2l. The higher the score, the worse the quality of sleep.

Study Procedures

The subjects were evaluated for psychiatric diagnosis, drug use history, and clinical scales. They were recording the primary clinical information. At 6:00 am, the subjects were collected 5ML of peripheral venous blood on an empty stomach, and all blood samples were stored at a temperature of −20°C for subsequent testing.

Quantitative Measurement of miR-124, IQGAP1 MRNA

After extracting RNA from whole blood, use EntiLink™ 1st Strand cDNA Synthesis Kit (ELK Biotechnology, EQ003) to synthesize first-strand Cdna, and use EnTurbo™ SYBR Green PCR SuperMix Kit (ELK Biotechnology, EQ001) for synthesis Real-time fluorescent quantitative PCR detection. The mRNA primers were synthesized by Wuhan Jinkairui Biological Engineering Co., Ltd., using GAPDH as the internal control. Small nuclear RNA U6 snRNA was used as the internal control. Fold change analyses were performed following the $2^{-\Delta\Delta Ct}$ method (6).

Dual-Luciferase Reporter Assay

To verify whether miR-214 directly targets IQGAP1, firstly, constructing the pGL6-IQGAP1 vector. The IQGAP1 target gene was synthesized by ELK biotechnology company. The IQGAP1 was amplified by PCR and connected to the overlapping sequence of the vector, and then recombined with the digested vector. The relevant information is as follows:

IQGAP1 5′-3′ primer sequences:

IQGAP1 Forward: CCGTGTAAAGATCCGGTACCCAGAGAGACAATTCACTCCA.

IQGAP1 Reverse: CTCCTCGAGGATATCGGATCCAAAGTGTATGACTTTTTATC.

miRNA Sequence: CCGUAAGUGGCGCACGGAAU.

PCR was amplified by denaturation, annealing, and extension procedures. After 30 min of recombination reaction at 37°C, high-efficiency DH5a competent cells were used for transformation. After 1 day, single clones were picked for sequencing detection, and single colonies with correct sequencing were used for seed preservation and endotoxin-free plasmid extraction. Next, the cells are grouped and prepared, and the cells are grouped as follows: (a) NC; (b) pGL6-miR-IQGAP1- WT 3′UTR-+pRL-TK; (c) pGL6-miR-IQGAP1- WT 3′UTR+mimics-NC+ pRL-TK; (d) pGL6-miR-IQGAP1- WT 3′UTR+miR-124-3p+pRL-TK;(e) pGL6-miR-IQGAP1-mut-3′UTR + pRL-TK; (f) pGL6-miR-IQGAP1-mut-3′UTR+mimics-NC+ pRL-TK; (g) pGL6-miR-IQGAP1-mut-3′UTR+ miR-124-3p + pRL-TK. Subsequently, the preparation of the transfection complex was carried out, and the dual-luciferase reporter gene detection was carried out after transfection, in the case of using Renilla luciferase as the internal control, the RLU value of firefly luciferase assay was divided by the RLU value of Renilla luciferase assay.

Statistical Analysis

Our study's statistical software package used for statistical calculations is the Statistical Program for Social Sciences (SPSS, version 22.0). We used the analysis of variance (ANOVA) and Chi-square test to compare the two groups' demographic data and clinical data. Spearman was used for correlation analysis, Bonferroni correction was used to adjust for multiple tests, and the Bonferroni-corrected indicators were included in the stepwise logistic regression, to determine the independent influencing factors that affect OASI score and MOCA score. Statistical significance was accepted when $P < 0.05$.

RESULTS

Comparison of Demographic and Clinical Variables Between the Morphine Dependence Group and the Control Group

A total of 40 patients with morphine dependence were included. The average intake in the past year was 4,564 mg/week, and the median OASI score was 32 points. The demographic data and clinical variables of the two groups were compared, the results showed that compared with the control group, the GAD-7 score ($Z = -6.499$, $P < 0.001$), PHQ-9 score ($Z = -7.621$, $P < 0.001$), PSQI score was found to be increased in the morphine dependence group, the MOCA score ($Z = -7.557$, $P < 0.001$) was found to be decreased in the morphine dependence group; the level of miRNA-124 ($Z = -3.017$, $P < 0.001$) was higher than the control group, and the level of IQGAP1 ($Z = -3.999$, $P < 0.001$) was lower than the control group. The above indicators were corrected by Bonferroni (Bonferroni corrected $P < 0.05/13 = 0.0038$). There was no statistically significant difference among other indicators (**Table 1**).

TABLE 1 | Comparison of demographic and clinical variables between morphine-dependent and control groups.

Characteristics	Control group	Morphine dependent group	Z/X^2	*p*
Age (years)	41.5 (28.00, 51.25)	36.00 (29.00, 47.00)	−0.539	0.590
BMI	21.5 (20.15, 23.18)	22.25 (20.49, 26.73)	−1.830	0.067
GAD-7 score	0.00 (0.00, 0.75)	9.00 (3.75, 14.75)	−6.499	<0.001
PHQ-9 score	0.00 (0.00, 0.75)	13.50 (7.25, 18.75)	−7.621	<0.001
MOCA score	30.00 (30.00,30.00)	26.00 (24.00, 29.00)	−7.557	<0.001
PSQI score	0.00 (0.00, 0.00)	16.50 (13.00, 18.00)	−7.932	<0.001
miRNA-124	0.40 (0.18, 0.69)	0.99 (0.45, 1.37)	−3.017	0.003
IQGAP1	1.68 (1.03, 2.28)	0.97 (0.60, 1.34)	−3.999	<0.001
OASI score	-	32.00 (25.75, 37.00)		
Average intake in the past year	-	4564.00 (2650.00, 7000.00)		
Male, *N* (%)	35 (87.5%)	35 (87.5%)	0.000	1.000
Education, *N* (%)			2.656	0.448
Junior high school	10 (25.0%)	11 (27.5%)		
Senior high school	14 (35.0%)	17 (42.5%)		
College	16 (40.0%)	11 (27.5%)		
Postgraduate	0 (0.0%)	1 (2.5%)		
Smoking	33 (82.5%)	35 (87.5%)	0.392	0.531
With physical disease	19 (47.5%)	14 (35.0%)	1.289	0.256

GAD-7 Score, The Generalized Anxiety Disorder Scale Score; PHQ-9 Score, Patient Health Questionnaire-9 Score; MOCA Score, Montreal Cognition Assessment Scale Score; PSQI Score, Pittsburgh Sleep Quality Index Score; OASI Score, Opioid Addiction Severity Inventory Score.

TABLE 2 | Correlation analysis of OASI and MOCA total score in morphine-dependent patients[a].

	1	2	3	4	5	6	7	8	9	10	11	12
1. OASI	1	−0.384	0.605	−0.597	0.291	0.377	0.228	−0.077	0.223	0.153	0.013	0.508
2. MOCA	0.014	1	−0.578	0.486	−0.092	−0.361	−0.499	0.065	−0.026	0.167	0.003	−0.382
3. miRNA-124	<0.001	<0.001	1	−0.530	0.090	0.337	0.446	−0.315	−0.036	−0.241	−0.010	0.401
4. IQGAP1	<0.001	0.001	0.000	1	0.082	−0.288	−0.340	0.039	−0.174	0.097	−0.239	−0.416
5. BMI	0.077	0.581	0.589	0.625	1	−0.217	0.050	−0.108	−0.082	0.114	−0.021	0.228
6.GAD-7	0.016	0.022	0.033	0.072	0.191	1	0.278	0.150	0.217	0.189	−0.062	0.374
7.PHQ-9	0.158	0.001	0.004	0.032	0.765	0.082	1	−0.106	−0.013	−0.247	0.236	0.365
8.PSQI	0.636	0.692	0.048	0.809	0.520	0.356	0.513	1	0.231	0.178	−0.036	−0.094
9.Gender	0.166	0.871	0.825	0.284	0.626	0.179	0.936	0.152	1	0.095	−0.086	−0.062
10. Age	0.347	0.304	0.134	0.550	0.497	0.243	0.124	0.272	0.560	1	−0.043	0.049
11. Smoking	0.936	0.984	0.952	0.137	0.899	0.702	0.142	0.824	0.599	0.794	1	0.194
12. Average intake in the past year	0.001	0.015	0.010	0.008	0.168	0.017	0.021	0.564	0.702	0.765	0.230	1

GAD-7 Score, The Generalized Anxiety Disorder Scale Score; PHQ-9 Score, Patient Health Questionnaire-9 Score; MOCA Score, Montreal Cognition Assessment Scale Score; PSQI Score, Pittsburgh Sleep Quality Index Score; OASI Score, Opioid Addiction Severity Inventory Score.

[a]*Correlation matrix: each cell in the table shows the correlation between two variables. The line of 1 s going from the top left to the bottom right is the main diagonal. The number in each cell on the upper right part of the diagonal represents the correlation coefficient (r), while and the number in each cell on the lower left part is the corresponding p value, which is a mirror image of those above the diagonal.*

Correlation Analysis of OASI and MOCA Total Scores in Patients With Morphine Dependence

The results of correlation analysis between OASI scores and MOCA scores in patients with morphine dependence found that the miR-124 levels ($r = -0.384$, $P < 0.001$), the IQGAP1 levels ($r = -0.597$, $P < 0.001$), GAD-7 scores ($r = 0.377$, $P = 0.016$), the average intake in the past year ($r = 0.508$, $p = 0.001$) were related to OASI scores, but GAD-7 scores were not corrected by Bonferroni (Bonferroni corrected $P < 0.05/11 = 0.0045$). The miR-124 levels($r = -0.578$, $P < 0.001$), the IQGAP1 levels ($r = 0.486$, $P = 0.001$), GAD-7 scores ($r = -0.361$, $P = 0.022$), PHQ-9 scores ($r = -0.499$, $P = 0.001$), the average intake in the past year ($r = -0.382$, $P = 0.015$) were related to the MOCA scores, but GAD-7 scores and the average intake in the past year did not pass Bonferroni

TABLE 3 | Linear regression analysis: analysis of independent influencing factors of OASI score.

Variables	B	Std.error	β	*p*	95% CI
miRNA-124	3.880	1.462	0.385	0.012	0.915 to 6.844
IQGAP1	−5.883	2.534	−0.346	0.026	−11.022 to 0.743
Average intake in the past year	3.440×10^5	0.000	0.078	0.558	0.000 to 0.000152

OASI Score, Opioid Addiction Severity Inventory Score.

TABLE 4 | Linear regression analysis: analysis of independent influencing factors of MOCA score.

Variables	B	Std.error	β	*p*	95% CI
miRNA-124	−1.618	0.565	−0.423	0.007	−2.764 to 0.471
IQGAP1	1.420	0.972	0.220	0.153	−0.552 to 3.392
Average intake in the past year	−0.081	0.062	−0.180	0.199	−0.205 to 0.044

MOCA Score, Montreal Cognition Assessment Scale Score.

correction (Bonferroni corrected $P < 0.05/11 = 0.0045$) (**Table 2**).

Independent Influencing Factors of OASI Score in Patients With Morphine Dependence

Including meaningful indicators in the correlation analysis with the OASI total score in the multiple linear regression model, the results showed that the miR-124 level ($B = 3.880$, $P = 0.012$) and the IQGAP1 level ($B = -5.883$, $P = 0.026$) were independent factors influencing the severity of morphine dependence in patients with morphine dependence (**Table 3**).

Independent Influencing Factors of MOCA Score in Patients With Morphine Dependence

Including meaningful indicators in the correlation analysis with the MOCA score into the multiple linear regression model, the results showed that the level of miR-124 ($B = -1.618$, $P = 0.007$) was an independent factor influencing the severity of cognitive impairment in patients with morphine dependence (**Table 4**).

Bioinformatics Software Predicts That IQGAP1 Is a Potential Target Gene of miR-124

The binding of miR-124 and IQGAP1 was analyzed by bioinformatics, and the results are shown in **Figure 1**. The results showed that miR-124 and IQGAP1 have complementary sequences that directly bind (**Figure 1**).

Dual-Luciferase Reporter Gene to Detect the Binding of miR-124 and IQGAP1

The dual-luciferase reporter gene detects the binding of miR-124 and IQGAP1. First, in the NC group and Mimics-NC group, there was no statistically significant difference in luciferase activity between IQGAP1WT and IQGAP1Mut ($P > 0.05$). In addition, in the miR-124-3p mimic group, the luciferase activity of IQGAP1WT was significantly lower than that of IQGAP1Mut, and the difference was statistically significant ($P < 0.05$). The above result indicates that miR-124-3p directly binds with IQGAP1 (**Table 5**).

DISCUSSION

This is the first time the mood, addiction, and cognitive function of miR-124 and its target protein in morphine-dependent patients has been studied. Our results show that morphine-dependent patients had higher GAD-7 scores, PHQ-9 scores, PSQI scores, and lower MOCA scores. They also had higher miR-124 levels and lower IQGAP1 levels. MiR-124 and IQGAP levels may predict the severity of dependence in morphine-dependent patients. MiRNA-124 levels may affect the degree of cognitive impairment in morphine-dependent patients.

The mechanisms related to the susceptibility of morphine-dependent patients and the emotional and cognitive impairment caused by morphine have not been fully revealed. MiRNAs and their target proteins may play an important role; miR-133, miR-146a, and miR-101 have been studied in the past. MiR-124 was found to be elevated in morphine-dependent patients in our study. This may be due to the activation of the NF-κB pathway by morphine, resulting in P65 binding to the promoter of miR-124 and promoting the transcription of miR-124. Qiu et al. found that acute morphine treatment could temporarily up-regulate the expression of P65 cells and then initiate the expression of miR-124 (15). The level of IQGAP1 decreased may be related to the conserved binding site of miR-124 in the 3′untranslated region (UTR) of IQGAP1. Our research and Fan et al. showed that induced mutations in the 3′untranslated region of IQGAP1 led to miR-124-mediated luciferase activation (16). This suggests that the miR-124 binding site in IQGAP1 is related to the down-regulation of IQGAP1. The increase of GAD-7 score, PHQ-9 score, and PISQ score in morphine-dependent patients may be related to morphine-induced anxiety and depression. The altered expression of dopamine receptors in the reward system may be related to morphine-induced anxiety. Vousooghi et al. showed that morphine-treated male offspring exhibited more anxiety-like behaviors and significantly increased D1 and D5 dopamine receptors in the prefrontal cortex and nucleus accumbens. Hippocampal D5 and D2 receptors decreased. The expression of the D4 dopamine receptor was raised in the striatum and hippocampus and decreased in the prefrontal cortex (17). In addition, some functional studies have also explored the causal relationship between miRNA expression and anxiety and depression-like behaviors. In animal models, the observed up-regulation or down-regulation of candidate miRNAs at important nodes of anxiety neural circuits can regulate anxiety-related behaviors. These identified miRNAs are related to specific neurotransmitter/neuromodulating signals, neurotrophic factor expression, synaptic plasticity, and stress regulation/hypothalamic-pituitary-axis function (18). Yang et al.

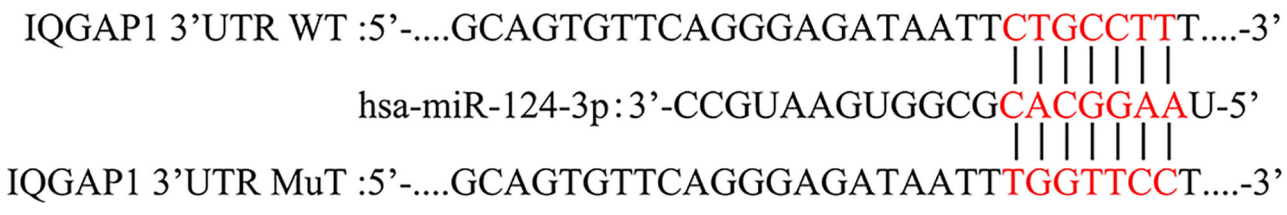

FIGURE 1 | Bioinformatics software predicts that IQGAP1 is a potential target gene of miR-124. The binding sites of Mir-124 to IQGAP1.

TABLE 5 | The dual-luciferase reporter gene detects the binding of miR-124 and IQGAP1.

Group	IQGAP1WT(x ± s)	IQGAP1Mut(x ± s)
NC	1.15 ± 0.1	1.15 ± 0.15
Mimics-NC	1.05 ± 0.11	1.1 ± 0.04
miR-124-3p mimics	0.46 ± 0.03	1.1 ± 0.16

In the miR-124-3p mimic group, the luciferase activity of IQGAP1WT was significantly lower than that of IQGAP1Mut, wt, wild type; mut, mutant.

found that knocking down miR-124 can improve the depression-like behavior of rats, which may be related at least in part to the up-regulation of CREB1 and BDNF expression in the hippocampus (19), under the influence of anxiety and depression symptoms, sleep quality declines. All in all, these data showed that miR-124 plays a vital role in genetic markers and symptoms of anxiety and depression in morphine dependence.

In this study, the OASI score is correlated with miR-124, IQGAP1, and morphine intake in the past year, and the levels of miR-124 and IQGAP1 are independent factors influencing the severity of morphine dependence in morphine-dependent patients. The basic mechanisms of opioid dependence and tolerance are complex changes in the levels of cells, synapses, and circuits in the central nervous system, as well as receptor phosphorylation, signal transduction, multimerization, etc. The enhancement of tolerance in the body also promotes the use of drugs, thereby increasing the formation of addictive behaviors. The administration of morphine can cause changes in the expression levels of multiple miRNAs in nerve tissues or cells. The miRNAs regulation model is transcription degradation or translation inhibition; its changes will affect the constitutive suppression of genes, which is essential for maintaining addictive behaviors (1). Studies have pointed out that after exogenous miR-124 supplementation *in vitro* (20), the neuronal differentiation level and glutamate transporter expression of human neural progenitor cells increase. Neuropathic pain and bone cancer pain-induced reduction of miR-124 in the brain and spinal cord of rats triggers microglial activation, leading to persistent hyperalgesia, which can be prevented by intrathecal administration of miR-124, so we speculate that miR-124 may be involved in the formation of morphine tolerance (21, 22). In other studies on the use of addictive substances, it has been found that the increase in peripheral blood miR-124 in cocaine-addicted women may be related to metabolism. In the research of alcohol use disorder, the rise of miR-124 can affect the alcohol intake behavior of mice by adjusting the HPA axis (23). Neurogenic differentiation (NeuroD) is critical for the development of both the central nervous system and the endocrine system. NeuroD is an important transcription factor during neurogenesis in the subgranular region of the adult hippocampus, regulating neural stem cell differentiation and migration. NeuroD also helps stabilize existing brain circuits and supports the formation of new circuits. Studies have found that miR-124 may regulate opioid addiction by affecting NeuroD-related pathways (24), and miR-124 interacts with the binding site of NeuroD1, which negatively regulates the expression of the preneural marker NeuroD1 (25). Morphine tolerance is an adaptive process thought to result from complex alterations in μ-opioid receptors (MORs) at the molecular level as well as at the synaptic, cellular and circuit levels, both in the peripheral and central nervous systems, where MORs are downregulated and neural adaptation may be the main mechanism of morphine tolerance (26). However, there are few independent studies on the function of miR-124 on MORs. Previous studies on the relationship between MORs and miRNAs found that miR-23b can complementarily bind to the 3′-UTR of MOR mRNA and reduce the expression of MOR at the post-transcriptional level. *In vitro*, chronic morphine exposure increased the expression of miR-339-3p in mouse hippocampal neurons, by binding to the 3′-UTR-specific sequence partially reversed by the miR-339-3p inhibitor, leading to the destabilization and degradation of MOR mRNA. However, it has also been reported that miR-16 can attenuate the translation of MOR mRNA, and morphine can upregulate MOR levels by inhibiting the expression of miR-16, but this finding originates from a study of CEM 174 cells (a lymphocyte lineages), but not on the nervous system (27). Our study found that patients' morphine addiction severity scores were positively correlated with miR-124, which led to speculation that long-term chronic morphine intake up-regulated the expression of miR-124 and that miR-124 was partially complementary to and bound to the 3′UTR of MORs mRNA. Thus, the translation of MORs was stopped, resulting in a decrease in MOR biosynthesis, aggravation of morphine tolerance, and an increase in morphine intake and dependence. As a direct target and influencing factor of miR-124, IQGAP1 also has a certain relationship with addiction and dependence. Sun et al. found that in primary rat and human cardiomyocytes, Methamphetamine (METH) exposure decreased the expression of primary rat

cardiomyocytes and the downstream protein IQGAP1 *in vivo* (9). Studies have found that local translational control in the spine is a powerful mechanism for regulating morphological and functional plasticity; miRNAs are involved in dendritic spine morphogenesis and development and addiction (28). Chronic morphine treatment causes the dendritic spines of the hippocampal neuron culture to collapse. Because overexpression of Rac1 can induce the formation of dendritic spines, IQGAP1 can bind to Rac1 as a junction (integrating receptor signals) and a node (diversifying signals to multiple out-puts), improve dendritic spine collapse, adjust dendritic morphology, reshape actin cytoskeleton, affect synapse formation, adjust the sensitivity of reward pathways, change neuronal plasticity, and then affect the formation of morphine dependence (29). However, due to limited research on substance-dependent genes and their target proteins, more mechanisms remain to be discovered. In general, combined with our findings that miR-124 and IQGAP1 are involved in regulating the addiction and tolerance of morphine-dependent patients, the meaningful indicators in the OASI correlation analysis were incorporated into the multiple linear regression model, and it was found that miR- 124 and IQGAP1 are not only related to the severity of morphine dependence, but also can be used as independent influencing factors to affect the severity of morphine dependence in patients with morphine dependence, and are not affected by other related factors, both can be used as markers of the nervous system and are involved in the formation of morphine addiction, tolerance and dependence.

In recent years, the epigenetic mechanism of learning and memory has been a hot spot in cognition-related research. Previous studies have shown that both IQGAP1 and miRNAs expressed in the brain are involved in human learning and memory. The disorder of miRNAs function may be related to the occurrence or progression of neurodegenerative diseases. Our study found that miR-124 and IQGAP1 are associated with the total score of MOCA. The level of miR-124 is an independent factor influencing the severity of cognitive impairment in patients with morphine dependence. This indicates that IQGAP1, as one of the target proteins of miR-124, can regulate and participate in cognitive function through the change of miR-124 level and other related mechanisms. MiR-124 can not only affect the cognitive level of patients together with its target protein, but also act as an independent factor affecting the patient's cognition. Studies found that miR-124 was predicted to control important target genes involved in neuronal apoptosis and neuronal stress-induced adaptation. The decline of cognitive function is also considered to be related to cell dysfunction and the increase of apoptotic factors. The overexpression of some miRNAs (such as miR-34, etc.) is involved in reducing the apoptosis rate of neurons, reducing cell dysfunction, and playing a neuroprotective role (30). Zhao et al. demonstrated that miR-124 exerts its neuroprotective effect on sevoflurane by targeting Capn4 and NF-κB signaling pathways, reducing hippocampal neuronal apoptosis (31). Hassouna et al. suggest that recombinant human erythropoietin (EPO) improves cognitive ability in neuropsychiatric disorders, which is associated with miR-124. In cultured nerve spheres, they found that EPO stimulates miR-124, related to late neuronal differentiation (32). MiR-124 may play a vital role in the normal prefrontal cortex. Kozuka et al. found that miR-124 dosing regulates prefrontal cortex function by inhibiting the Drd2 pathway (33). Neural function in the central nervous system is closely related to signal transduction; the specific cellular functions of signal transduction pathways depend to a large extent on the regional regulation of scaffold proteins. The N-cadherin/IQGAP1/Erk-2 signaling pathway affects cognition, emotion, and motivational behavior. Mice lacking the IQGAP1 gene have significantly reduced NR2A levels on the surface and impaired ERK activity, and the reduction in the number of the spine in IQGAP1 knockout mice is region-specific. The hippocampus and lateral amygdale that affect memory and emotion are the most affected, showing long-term potentiation (LTP) damage (11). Yang et al. found that IQGAP1 binding site polymorphism with miR-124 can influence human cognitive performance. They concluded that individuals carrying the derived T-allele had higher IQGAP1 expression in the brain than their ancestral A-allele carriers (6). Overall, these results demonstrated that miR-124 and its target protein IQGAP1 are involved in regulating cognitive function in patients with morphine dependence.

The current research is helpful to understand the pathogenesis of morphine dependence based on genetics, and the level changes of miRNAs and their target protein can also be used as targets for the diagnosis and treatment of morphine dependence in the future. But our research also has limitations. First, the number of enrolled cases is small, and the result does not rule out the possibility of false positives. The number of cases needs to be increased. Secondly, we only conducted a cross-sectional study, and it is not clear whether there are any changes in blood indicators in patients with morphine dependence. Moreover, when we collect patients, we focus on the abuse of morphine, but people who use addictive substances are often prone to smoking, drinking, and other problems. Whether these factors impact the results is also an issue that needs attention. In conclusion, our research found that compared with the control group, the expression of miR-124 and IQGAP1 in morphine-dependent patients is significantly different. The levels of miR-124 and IQGAP1 are correlated with anxiety and depression symptoms, miR-124 and its target protein IQGAP1 are involved in regulating addiction and cognitive function in patients with morphine dependence.

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 Ethics Committee of the First Affiliated Hospital of

Harbin Medical University. 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

JH and XiW: designed this research and revised the manuscript. JS: designed this research, performed the statistical analysis, and wrote the manuscript. YChi, YZ, and LT: collected data. YChe, CC, YD, HS, MC, LL, NZ, CK, XH, QL, XL, SZ, MN, HoW, LY, JLi, HuW, and JLu: organized the data. XuW: performed the statistical analysis. All authors contributed to the article and approved the submitted version.

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Buprenorphine reduces methamphetamine intake and drug seeking behavior *via* activating nociceptin/orphanin FQ peptide receptor in rats

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Buprenorphine, which has been approved for the treatment of opioid dependence, reduces cocaine consumption by co-activating μ-opioid receptors and nociceptin/orphanin FQ peptide (NOP) receptors. However, the role of buprenorphine in methamphetamine (METH) reinforcement and drug-seeking behavior remains unclear. This study investigated the effects of buprenorphine on METH self-administration and reinstatement of METH-seeking behavior in rats. We found that buprenorphine pretreatment had an inhibitory effect on METH self-administration behavior, and that buprenorphine at a dose of 0.3 mg/kg could inhibit motivation to respond for METH. Pretreatment with the NOP receptor antagonist thienorphine (0.5 mg/kg) or SB-612111 (1 mg/kg) could reverse the inhibitory effect of buprenorphine (0.1 mg/kg) on the METH self-administration. Moreover, treatment with buprenorphine (0.1 mg/kg and 0.3 mg/kg) significantly reduced the drug-seeking behavior induced by context or by METH priming but failed to reduce the drug-seeking behavior induced by conditional cues. Additionally, the NOP receptor antagonist SB-612111 reversed the inhibitory action of buprenorphine on the drug-seeking behavior induced by METH priming. The results demonstrated that buprenorphine reduced either METH intake or the drug-seeking behavior by activating NOP receptors, providing empirical evidence for the clinical use of buprenorphine in the treatment of METH relapse and addiction.

KEYWORDS

buprenorphine, nociceptin/orphanin FQ peptide, substance use disorder, opioid receptor, methamphetamine

Introduction

Methamphetamine (METH) is one of the most commonly used illegal drugs worldwide. According to recent estimates, approximately 35 million people worldwide use amphetamine-type stimulants, and the number of abusers continues to rise (1, 2). The National Drug Abuse Monitoring Annual Report (2016) reported that synthetic drug abusers accounted for 54.8% of the total drug abusers in China, with METH abusers alone accounting for 87.4% of all synthetic drug abusers (3). METH use not only causes damage to the physical and mental health but also leads to a series of socio-economic and judicial problems. To date, few medicines have had their effectiveness in treating METH use disorders or preventing relapse among METH users demonstrated with strong evidence (4). As a partial μ-opioid receptor (MOP) agonist, buprenorphine has been approved for the treatment of opioid dependence (5–8). In recent years, the use of buprenorphine has emerged in the treatment of cocaine addiction, even though only high doses of buprenorphine may have noticeable effects in suppressing the desire for cocaine (9) and reducing concomitant opiate and cocaine use (10). Sporadic clinical observations have suggested that buprenorphine also has an effect on METH use disorders. For example, one clinical trial has shown that 16 weeks of daily buprenorphine induce greater reductions in METH craving in 40 participants (11). Another clinical observation supports the efficacy and safety of buprenorphine as a short-term treatment for METH craving (12, 13).

In preclinical studies, buprenorphine effectively inhibited cocaine self-administration (14). Studies have shown that buprenorphine reduces cocaine intake and enhances dopamine release induced by cocaine (15), reduces cocaine-seeking behavior during extinction following acute cocaine priming injections (16), and blocks cocaine sensitization by increasing basal levels of glutamate expression in the nucleus accumbens (NAc) (17). Moreover, high-dose buprenorphine extended extracellular DA outflow in the caudate nucleus for 190 min, whereas low-dose buprenorphine reduced DA release. Both doses attenuated METH-induced DA peak effects (18). In addition to its classical MOP, delta opioid receptor (DOP), and kappa opioid receptor (KOP) bindings, buprenorphine also acts as an agonist and/or partial stimulator for the nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptor (19–21).

The NOP receptor is a G protein-coupled receptor, originally classified as belonging to the opioid receptor family (22). However, the endogenous ligands of other opioid receptors, including MOP, KOP, and DOP receptors, have little affinity for NOP receptor (23). N/OFQ and its NOP receptor are widely distributed in brain regions such as the ventral tegmental area (VTA) and the NAc, where both are largely co-expressed and may be involved in the control of drug dependence (24). Studies have found that endogenous N/OFQ activates NOP receptors to reduce the expression of cocaine (25, 26) or METH-conditioned place preference (CPP) (27). Intracranial injection of N/OFQ inhibits cocaine-induced DA release in the NAc, blocks cocaine-induced motor sensitization by activating NOP receptors (28), and attenuates METH-induced acute reward response (29) and METH withdrawal responses (30). Recently, evidence has shown that, through the co-activation of MOP and NOP receptors, buprenorphine is essential in reducing cocaine intake (14). Up to date, whether buprenorphine inhibit the METH self-administration and drug seeking behavior is still unclear.

Here we hypothesized that buprenorphine may exert an inhibitory effect on METH self-administration and cravings through its agonistic effects on NOP receptor. First, we observed systematically the effects of buprenorphine on METH self-administration behavior and motivation for METH. To elucidate this NOP receptor mechanism, we performed intensive pharmacological studies using NOP receptor antagonist thienorphine and SB-612111. Thienorphine, a novel analog of buprenorphine, acts as an antagonist at NOP receptor and an agonist at DOP, KOP and partial agonist at MOP (31). We could compare the pharmacology of buprenorphine and thienorphine in assay for METH reinforcement. We further observed the effects of buprenorphine on drug-seeking behavior induced by context after withdrawal, and on reinstatement of drug seeking behaviors induced by conditioned cues or METH priming in self-administered rats. Moreover, SB-612111, a selective NOP receptor antagonist (32), was used to determine whether buprenorphine mediates METH reinforcement and relapse through NOP receptor.

Materials and methods

Animals

Male Sprague–Dawley rats (n = 86) provided by the Experimental Animal Center of Zhejiang Province and weighing 280–300 g was used in the present study. The rats were housed in an airy and clean animal room under a 12-h light/12-h dark cycle (lights switched on at 8 a.m. and switched off at 8 p.m.) with constant temperature (22–24°C) and constant humidity (50–70%). Food and water were provided *ad libitum* in the home cage for all rats, but food for sucrose reinforcement rats at the beginning train was restricted. The experimental environment strictly complied with the regulations on the management of laboratory animals in China. The experimental procedures were approved by the Ethics Committee of the Laboratory Animal Use and Care of Ningbo University. All animal experiments were performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th Edition).

Drugs

Methamphetamine was obtained from the Drug Intelligence and Forensic Center of the Ministry of Public Security (Beijing, China) and was dissolved in 0.9% sterile saline. Buprenorphine Hydrochloride Injection was purchased from TIPR Pharmaceutical Co., Ltd. (Tianjin, China). Thienorphine (*N*-cyclopropylmethyl-7α-[(*R*)-1-hydroxy-1-methyl-3-(thien-3-yl)-propyl]-6,14-endo-ethanotetrahydronororipavine) was obtained from the Beijing Institute of Pharmacology (Beijing, China) and dissolved in 3% dimethyl sulfoxide (DMSO) and diluted in 0.9% sterile saline to a final concentration of 1% DMSO. SB-612111 was purchased from Sigma-Aldrich (St Louis, MO, USA), dissolved in 3% DMSO, and diluted in 0.9% sterile saline to a final concentration of 1% DMSO. Control animals received the same amount of 0.9% sterile saline or vehicle (1% dimethyl sulfoxide). Sucrose pellets were purchased from BioServe (Frenchtown, NJ).

Intravenous catheter surgery

All surgical procedures were performed with the animals under sodium pentobarbital anesthesia (50 mg/kg, i.p.) and the analgesic carprofen (5 mg/kg, s.c.) was given following surgery for two days. Rats were surgically implanted with a chronic intravenous indwelling catheter (33). The catheters were flushed daily with a 0.2 ml saline–heparin solution (25 U/ml heparin) to maintain catheter patency. To prevent infection, the rats were treated post-surgically with penicillin B (30 mg/kg, intramuscularly) every day. The animals were allowed to recover for at least 7 days. From the second week of training, catheter patency was tested by injecting 0.1 mL (10 mg/mL) of propofol through the catheter for sedation.

Methamphetamine self-administration

Rats were trained to self-administer METH in operant chambers equipped with two nose-poke ports (ENV-114 M, Med Associates, Lafayette, IN, USA). The training consisted in daily 4-h sessions for 10 consecutive days under a fixed-ratio 1 schedule of reinforcement, as previously described (34, 35). Rats received a single METH infusion (0.05 mg/kg) following an active nose poke. Each infusion was paired with a 5-s illumination of light in combination with the noise of the infusion pump; together, these stimuli served as a discrete conditioned cue paired with the drug infusion. Following the infusion, a time-out period was imposed for 20 s, during which the response was recorded but produced no programmed consequences. Responding to the inactive nose-poke port had no programmed consequences. The rats were returned to their individual housing cages shortly after the session. Similar to a previous report (36), the rats exhibited reliable METH self-administration when an acquisition criterion required that the subjects' active nose pokes varied by less than 10% over the course of three consecutive maintenance days. The apparatus was controlled using an IBM-compatible PC running a program written in Pascal (Borland Delphi 6.0). After the rats acquired the METH self-administration behavior for 10 days under the FR1 schedule, they were randomly assigned to five groups (n = 7 in each group) and injected with vehicle(saline), 0.01, 0.03, 0.1 or 0.3 mg/kg buprenorphine (s.c.) 15 min before the testing session.

To investigate the pharmacological mechanism by which buprenorphine inhibits METH reinforcement, we tested the two NOP antagonists in the present experiment. The SB-612111 concentration used for this study was chosen based on an effective *in vivo* dose at 1 mg/kg (32), and thienorphine concentration used at dose of 0.5 mg/kg based on its antinociceptive effect ED 50 value of 0.25 mg/kg (37). The rats were randomly assigned to six groups (n = 7 in each group) and injected with vehicle (saline plus 1% DMSO, s.c.), buprenorphine treated group (1% DMSO plus 0.1 mg/kg buprenorphine,s.c.), thienorphine treated group (0.5 mg/kg thienorphine plus saline, s.c.), SB-612111 treated group (1 mg/kg SB-612111 plus saline, s.c.) or another two groups with an injection of thienorphine (0.5 mg/kg, s.c.) or SB-612111 (1 mg/kg, s.c.) and 10 min later they received buprenorphine(0.1mg/kg, s.c.) administration. Testing of self-administration occurred at 15 min after the final drug injection.

Motivation to respond for methamphetamine

The METH motivation was measured by using progressive ratio (PR) schedule, a task that directly measures the breakpoint at which an animal is unwilling to further work for reward. The PR reinforcement schedule required animals to progressively increase nose poking for each successive reward in the following series within a self-administration session. There was a timeout of 20 s following the infusion in the PR schedule. The progression of response requirements was calculated using the following equation: Response ratio = (5 × e (0.2 × infusion number)) − 5), which was rounded to the nearest integer. The nose poking requirements were as follows: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, and 402. After METH self-administration training for 10 days under the FR1 schedule, the rats were randomly divided into five groups (n = 7 in each group) and injected (s.c.) with vehicle or buprenorphine at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, or 0.3 mg/kg at 15 min prior to the training session, when the training procedure was switched to the PR schedule for 4 h. The last successfully completed ratio was registered as the breakpoint for that session (38, 39).

Drug-seeking induced by context and reinstatement by conditioned cues or methamphetamine priming

After the rats were withdrew for 14 days in their individual housing cages after 14 days METH self-administration, the rats were divided into five groups (n = 7 per group) for receiving vehicle (saline, s.c.), buprenorphine (0.01, 0.03, 0.1, or 0.3 mg/kg, s.c.) to test the drug-seeking behavior induced by context for 2 hours. At 15 min after buprenorphine, rats were re-placed into the same training chambers without house light, LED light, or sound from the pump, and the intake of METH injections by touching the active nose poke. However, the computer recorded the number of active or inactive nose pokes.

The rats underwent 2 h extinction for 3 consecutive days to reduce the effect of context on reinstatement test. The extinction conditions consisted of only original training context, while the pump and lights being turned off. On the reinstatement test day, the rats was performed for 2h in which the rats were exposed to light and noise cues for 5 s at the start of the session, and each subsequent active nose poke previously paired with METH injection elicited a cue presentation without a METH injection for the rest of the test session. The doses of buprenorphine were used as same as described above.

The reinstatement of METH priming was carried out after another 3 consecutive days extinction, rats were administered METH (0.5 mg/kg, i.p.) 10 min before testing, and no conditioned cues were present during the 2-h testing session (36). Rats (n = 7 per group) were injected (s.c.) with buprenorphine at 0.01, 0.03, 0.1 mg/kg, or 0.3 mg/kg or vehicle 15 min prior to methamphetamine (0.5 mg/kg) to test the effect of buprenorphine on drug seeking induced by METH priming.

To elucidate the role of NOP receptor in the effects of buprenorphine on reinstatement of METH priming, four group of rats were injected with vehicle(saline plus 1% DMSO, s.c.), buprenorphine treated group(0.1 mg/kg buprenorphine plus 1% DMSO,s.c.), SB-612111 treated group (1mg/kg SB-612111 plus saline, s.c.), or both SB-612111 (1mg/kg, s.c.) and buprenorphine(0.1mg/kg, s.c.) at 15 min prior to methamphetamine (0.5 mg/kg, i.p.) administration.

Sucrose reinforcement

The standard procedure stipulated that during one training period, the rat obtained one sucrose pellet every time the nasal touch is correctly completed, and the training period is automatically terminated after 100 pellet deliveries or 1 h. Starting from FR1, when all rats completed 100 sucrose pellets in two training sessions, the FR was increased, and FR2, FR3, FR5, and FR10 sucrose intensive training periods were completed in sequence. Rats underwent one training session per day. After the rats acquired food self-administration under FR10 schedule for 10 days, they were randomly assigned to five groups (n = 6 in each group) and injected with vehicle,0.01, 0.03, 0.1, 0.3, and 1 mg/kg buprenorphine (s. c.) at 15 min before the testing session.

Statistical analysis

Data from the self-administration and reinstatement tests were analyzed by using one-way analysis of variance (ANOVA). Normal distribution and uniform variance were analyzed by Tukey-HSD for *post hoc* analysis between the groups and Games-Howell and LSD multiple comparisons were used for *post hoc* analysis. When the measurement data with uneven variance between the groups and LSD test for pairwise comparison. The mean number of infusions or responses for active and inactive holes during self-administration with FR schedule and the reinstatement by conditional cues and drug priming of METH were analyzed using one-way ANOVA with Tukey-HSD for *post hoc* analysis. The data of breakpoint under PR schedule, thienorphine treatment combined with buprenorphine for METH reinforcement, and sucrose reinforcement were analyzed by one-way ANOVA with Games-Howell. For the data of reinstatement by contextual cues, LSD test was used for pairwise comparison. Statistical significance was considered when the P-value was less than 0.05.

Results

Effect of buprenorphine on METH reinforcement and motivation

As shown in **Figure 1A**, self-administration of METH was successful after 10 days of training under the FR1 schedule. One-way ANOVA revealed a significant effect of buprenorphine treatment on active nose pokes ($F_{(4,\ 30)} = 13.752$, $P < 0.001$; **Figure 1B**), but not on inactive nose pokes ($F_{(4,30)} = 2.413$, $P = 0.071$; **Figure 1B**). As shown in **Figure 1C**, one-way ANOVA revealed that T the number of infusions of METH was reduced by buprenorphine treatment at doses ranging from 0.03 to 0.3 mg/kg ($F_{(4,\ 30)} = 16.637$, $P < 0.001$).

The effect of buprenorphine on METH motivation was examined under the PR schedule. One-way ANOVA revealed that buprenorphine significantly decreased the breakpoint of active responses ($F_{(4,\ 30)} = 4.602$, $P = 0.005$; **Figure 2A**). And at the dose of 0.3 mg/kg, buprenorphine decreased the last number of infusions under the PR schedule ($F_{(4,\ 30)} = 3.302$, $P = 0.023$; **Figure 2B**).

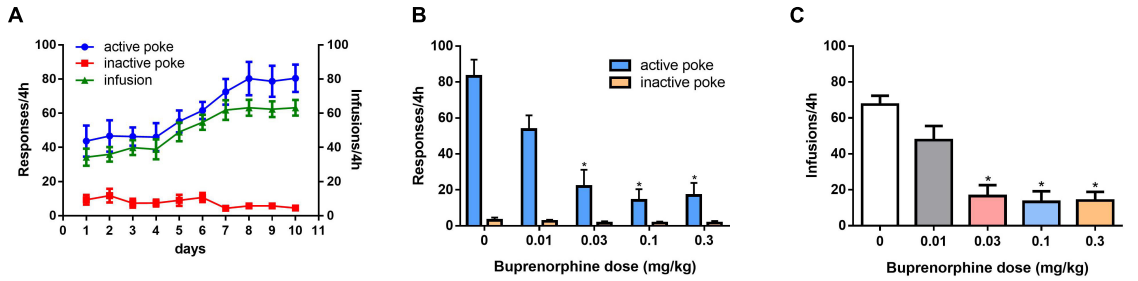

FIGURE 1
Effects of pretreatment with buprenorphine on methamphetamine reinforcement in rats. Values are presented as means ± SEM. **(A)** The acquisition of METH self-administration at dose of 0.05 mg/kg under FR1 schedule of reinforcement, left *Y* axis indicates the responses of nose poke and the right *Y* axis is the infusions. **(B)**. Buprenorphine inhibited the active responses in a dose-dependent manner on METH self-administration under FR1 schedule. **(C)**. Buprenorphine inhibited infusions on METH self-administration under FR1 schedule. *$P < 0.05$ vs. vehicle.

Effect of thienorphine or SB-612111 combined with buprenorphine on methamphetamine reinforcement

First, we observed the effect of thienorphine treatment on inhibitory action of buprenorphine on METH reinforcement. One-way ANOVA revealed the main effect of active pokes ($F_{(3, 24)} = 9.776$, $P < 0.001$; Figure 3A) and infusions among the four groups ($F_{(3, 24)} = 13.485$, $P < 0.001$; Figure 3B). As shown in Figures 3A,B, 0.1 mg/kg buprenorphine significantly reduced the number of active pokes and METH infusions ($P < 0.05$), but thienorphine alone was not able to reduce the number of active responses ($F = 4.20$, $P = 0.943$) and infusions ($F = 4.295$, $P = 0.976$). When thienorphine and buprenorphine were co-administered, the number of active responses and infusions increased significantly compared to buprenorphine alone (both $P < 0.05$). Inactive responses did not differ among the four groups ($F_{(3, 24)} = 2.955$, $P = 0.053$).

Next, we determined the effects of another NOP antagonist SB-612111 on inhibitory action of buprenorphine on METH reinforcement. One-way ANOVA revealed a significant main effect of active pokes ($F_{(3,24)} = 11.081$, $P < 0.001$, Figure 3C) and infusions ($F_{(3,24)} = 11.105$, $P < 0.001$; Figure 3D). Multiple comparisons showed that active pokes and infusions pretreated by buprenorphine decreased significantly compared with the vehicle ($P < 0.05$). However, no significant effect of SB-612111 alone on active pokes ($F = 0.87$, $P = 0.827$) or infusions ($F = 2.51$, $P = 0.458$) was observed. When SB-612111 and buprenorphine co-administered, the active pokes ($F = 8.182$, $P = 0.009$) and infusions ($F = 10.438$, $P = 0.004$) were significantly increased compared with those in the buprenorphine alone. There were no differences in the inactive responses among the four groups ($F_{(3,24)} = 2.980$, $P = 0.051$; Figure 3C).

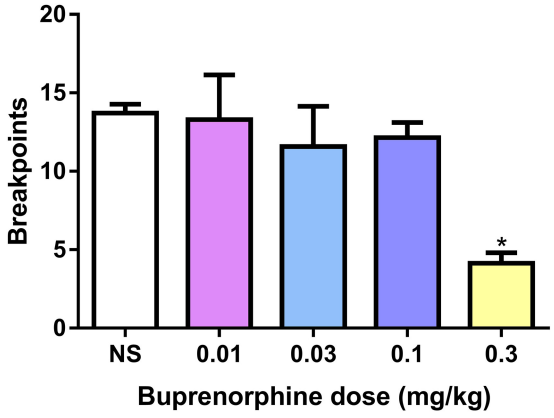

FIGURE 2
Effects of buprenorphine on the motivation for methamphetamine use. The motivation for methamphetamine use expressed as the breakpoint reached under a progressive-ratio schedule of reinforcement. Values are presented as means ± SEM. *$P < 0.05$ vs. vehicle.

Effect of buprenorphine on drug-seeking induced by context and reinstatement of conditioned cues

We evaluated the effect of buprenorphine on context-induced drug-seeking behavior after withdrawal for 14 days. As shown in Figure 4A, one-way ANOVA revealed significant effect of buprenorphine on the active nose pokes ($F_{(4,30)} = 3.559$, $P = 0.017$), the multiple comparison showed that the active responses were reduced by buprenorphine at the doses of 0.1,0.3 or 1 mg/kg (all $P < 0.05$), while the inactive nose pokes were not significantly different among the groups ($F_{(4,30)} = 2.203$, $P = 0.093$). This indicated that buprenorphine inhibited in a dose dependent manner drug-seeking behavior induced by contextual cue.

After 3 days of extinction, the rats were tested to evaluate the effects of reinstatement of METH seeking induced by

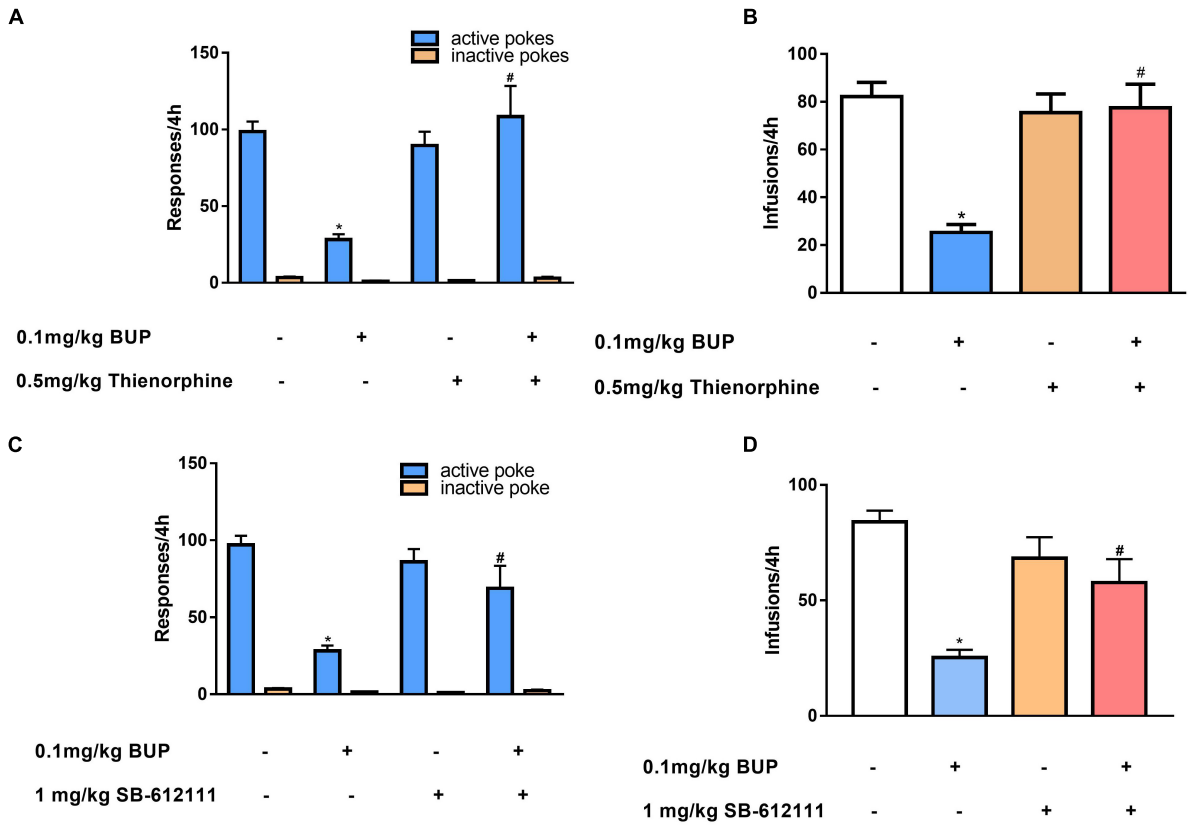

FIGURE 3
Effects of thienorphine and SB-612111 on inhibitory action of buprenorphine on methamphetamine self-administration. Data are presented as means ± SEM. The effects of thienorphine pretreatment (0.5 mg/kg, s.c.) with buprenorphine on active or inactive response **(A)** and total infusions **(B)** during METH self-administration under FR1 schedule of reinforcement. Buprenorphine reduced the active responses and infusions, thienorphine combined with buprenorphine reversed the inhibitory action of buprenorphine, but thienorphine alone did not affect the responses and infusions. The effects of SB-612111 pretreatment (1mg/kg, s.c.) with buprenorphine on the responses **(C)** and METH infusions **(D)**. SB-612111 reversed the inhibitory action of buprenorphine on the active responses and METH infusions, but it alone failed to affect the responses and infusions. *$P < 0.05$ vs. vehicle treatment, #$P < 0.05$ vs. buprenorphine alone.

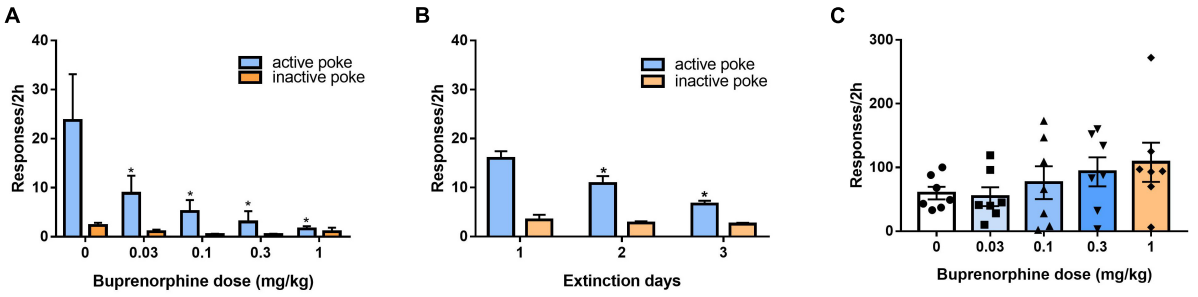

FIGURE 4
Effect of buprenorphine on drug-seeking induced by cues. **(A)** Buprenorphine pretreatment reduced the active responses induced by context during 2 h test in the training chamber after withdrawal from METH self-administration for 14 days. *$P < 0.05$ vs. vehicle treatment. **(B)** The rats were extinguished for 3 days. *$P < 0.05$ vs. first day extinction. **(C)** The reinstatement induced by conditioned cues. Buprenorphine did not inhibit the active responses induced by conditional stimulus cues during 2 h test. Data are presented as means ± S.E.M.

conditioned cues. As shown in Figure 4B, one-way ANOVA revealed significant effect of extinction (days) on the active responses ($F_{(2,102)} = 12.806$, $P < 0.001$) but no effect on the inactive responses ($F_{(2,102)} = 0.518$, $P = 0.597$). As shown in Figure 4C, buprenorphine tended to increase the active responses, but one-way ANOVA revealed no significant main

effect of buprenorphine on the active responses ($F_{(4,30)} = 1.048$, $P = 0.399$) or inactive nose pokes ($F_{(4,30)} = 2.665$, $P = 0.052$).

Effects of SB-612111 combined with buprenorphine on reinstatement of methamphetamine priming

After 3 days of additional extinction (Figure 5A), the rats were tested to observe the effects of buprenorphine on reinstatement of METH priming. One-way ANOVA revealed significant effect of extinction (days) on the active responses ($F_{(2,102)} = 21.617$, $P < 0.001$) but no effect on the inactive responses($F_{(2,102)} = 0.984$, $P = 0.377$). As shown in Figure 5B, one-way ANOVA revealed a significant main effect of buprenorphine on the active nose pokes ($F_{(4,30)} = 7.134$, $P < 0.001$) but not the inactive nose pokes ($F_{(4,30)} = 1.710$, $P = 0.714$). Multiple comparisons indicated that METH administration could significantly increase the active responses compared to that of vehicle group ($P < 0.05$), indicating that METH priming induces the reinstatement of drug seeking behavior. Additionally, buprenorphine at the doses of 0.3 to 1 mg/kg significantly decreased the active responses compared to that of METH primed group ($P < 0.05$).

After another 3 days of extinction (Figure 5C), the rats were tested to observe the effects of SB-612111 combined with buprenorphine on reinstatement of METH priming. One-way ANOVA revealed significant effect of extinction (days) on the active responses ($F_{(2,81)} = 23.161$, $P < 0.001$) but no effect on the inactive responses ($F_{(2,81)} = 4.045$, $P = 0.105$). As shown in Figure 5D, one-way ANOVA revealed the main effect of SB-612111 combined with buprenorphine on the active nose pokes ($F_{(3,21)} = 5.627$, $P = 0.005$), whereas the inactive nose pokes were not significantly different among four groups ($F_{(3,21)} = 1.802$, $P = 0.714$). Multiple comparisons indicated that buprenorphine at 0.1 mg/kg significantly decreased the active responses compared with the vehicle ($F = 6.700$, $P = 0.049$) and the combination administration of SB-612111 with buprenorphine increased the active responses compared with buprenorphine alone ($F = 8.413$, $P = 0.03$). However, SB-612111 alone failed to affect the active responses ($F = 1.766$, $P = 0.686$).

Effect of buprenorphine on sucrose reinforcement

To determine whether buprenorphine specifically affected METH reinforcement, the effect of buprenorphine on sucrose self-administration was examined in a separate set of rats. As shown in Figure 6, one-way ANOVA revealed a significant effect of buprenorphine on the responses ($F_{(5,36)} = 10.999$, $P < 0.001$) and sucrose pellets ($F_{(5,36)} = 10.793$, $P < 0.001$). Multiple comparisons indicated that buprenorphine significantly reduced the responses and total number of sucrose pellets only at the doses of 0.3 mg/kg (both $P < 0.05$).

Discussions

The present findings showed that buprenorphine pretreatment reduced the rewarding effect, total consumption, and rewarding motivation of METH, and this effect was reversed by the NOP receptor antagonists thienorphine and SB-612111. Moreover, buprenorphine inhibited the drug-seeking behavior induced by context or METH priming but failed to reduce the drug-seeking behavior induced by conditioned cues. The inhibitory action of buprenorphine on METH priming-induced drug-seeking behavior was reversed by the NOP receptor antagonist SB-612111. These results demonstrated that buprenorphine not only attenuated the METH self-administration but also the relapse into drug-seeking behavior through the activation of NOP receptor.

Buprenorphine is widely used to treat opioid addiction (40) and also blocks the action of exogenous opioids, thereby reducing the use of illegal opioids (41). The present results showed that low-dose buprenorphine treatment inhibited METH self-administration and total intake doses of METH in rats. Evaluating the dose effects of buprenorphine on food rewards indicated that small doses of buprenorphine were unlikely to inhibit natural rewards. Moreover, the evidence have shown that BUP at 0.1 mg/kg significantly increases locomotor activity compared to vehicle controls (42), METH and buprenorphine has no effects on locomotor activity in the open field test (43). This suggested that buprenorphine at lower doses may have a specific inhibitory effect on METH reinforcement and consumption. Albeit buprenorphine reduced incentive motivation for METH at 0.3 mg/kg, this dose of buprenorphine also inhibited the sucrose reinforcement, indicating no specific effect of buprenorphine on motivation for METH.

Under normal circumstances, DA is released and the DA transporter (DAT) on the presynaptic membrane can reuptake DA to maintain it at a stable concentration in the synaptic cleft (44). METH, as a pseudo-neurotransmitter, can bind with DAT, resulting in the uncontrolled release of DA in the NAc (45). As the reuptake of DA is inhibited, the DA content in the synaptic cleft sharply increases, with the eventual exhaustion of DA during long-term METH exposure (46). Buprenorphine is a partial agonist of MOP, an antagonist of DOP and KOP (47), and a low-affinity partial agonist of the NOP receptor (19, 48). Studies have shown that MOR agonists can modulate the activity of dopamine neurons, thus altering the pharmacodynamic effects of METH on the dopaminergic system (49). Buprenorphine attenuates the METH-induced DA peak effect, and at low doses, it reduces METH-induced DA release (18). Buprenorphine prevents acute novelty stress-induced blunting of DA levels and approach behavior for

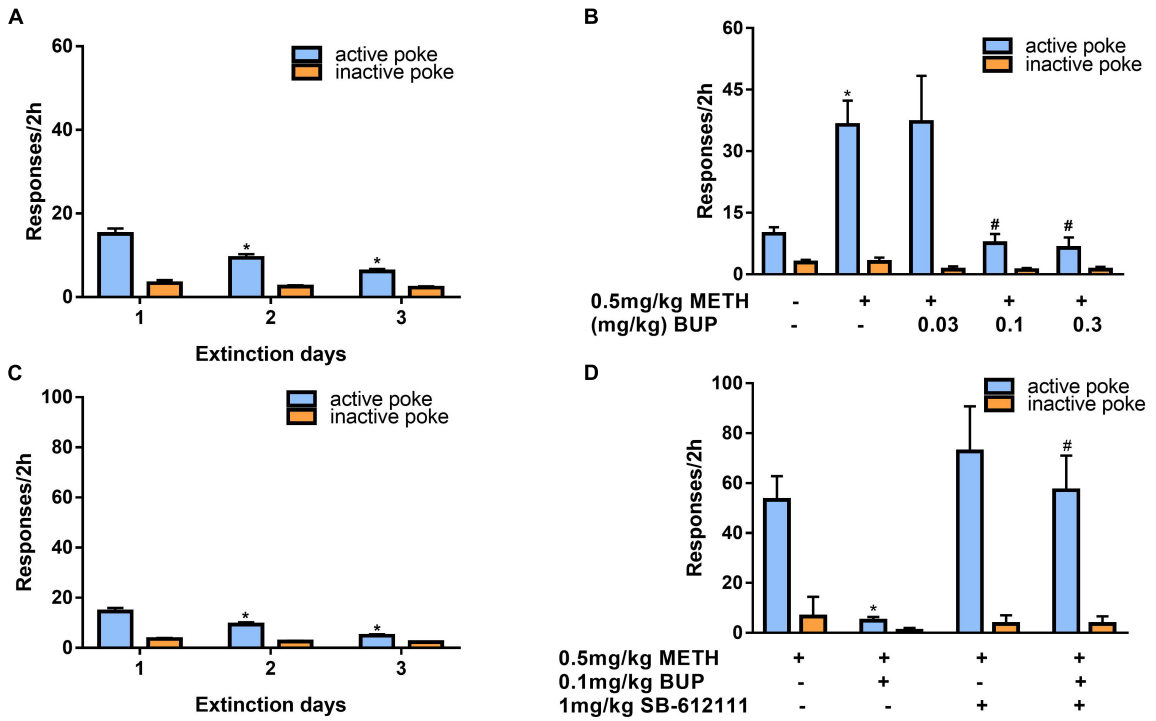

FIGURE 5
Effects of buprenorphine or SB-612111 combined with buprenorphine on drug-seeking induced by METH priming in rats. **(A)** The rats were extinguished for 3 days. *$P < 0.05$ vs. first day extinction. **(B)** Effects of buprenorphine on drug-seeking behavior induced by METH priming. The active responses increased significantly after administration of METH and buprenorphine inhibited the active responses in a dose-dependent manner. *$P < 0.05$ vs. vehicle, #$P < 0.05$ vs. buprenorphine alone. **(C)** The rats were extinguished for 3 days. *$P < 0.05$ vs. first day extinction. **(D)** Effects of SB-612111 combined with buprenorphine on drug-seeking behavior induced by METH priming. SB-612111 pretreatment reversed the inhibitory action of buprenorphine on active responses induced by METH priming, but it alone failed to affect the active responses. Data shown are means ± S.E.M. *$P < 0.05$ vs. METH priming, #P < 0.05 vs. buprenorphine treatment.

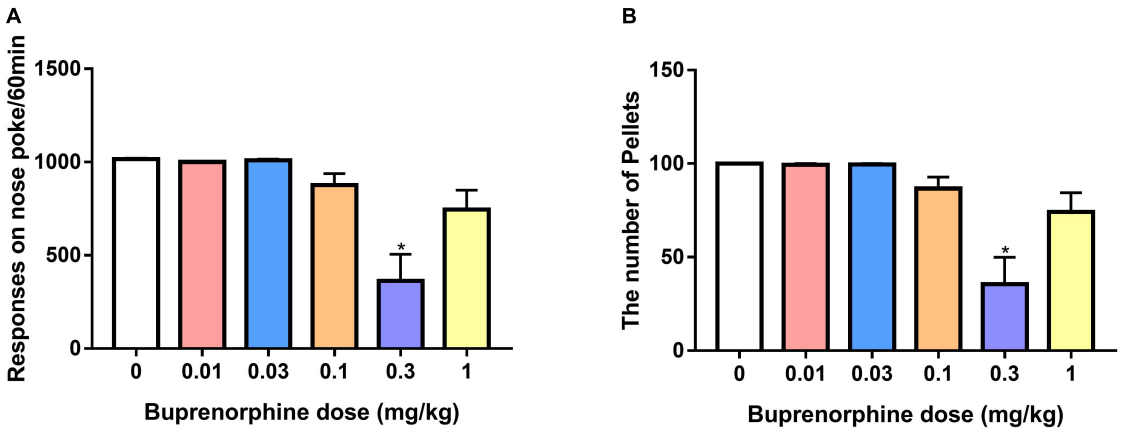

FIGURE 6
Effect of buprenorphine on sucrose self-administration. Data are presented as means ± SEM. **(A)** The effect of buprenorphine on the responses of nose pokes under FR10 schedule. **(B)** The effect of buprenorphine on the number of sucrose pellets. Only buprenorphine at dose of 0.3 mg/kg inhibited the responses and sucrose pellets. *$P < 0.05$ vs. vehicle.

food reward (50). However, buprenorphine activates DA neurons in the VTA, but this activation is not reversed by the opioid antagonist naloxone (51). Buprenorphine also enhances basal levels of DA, attenuates the NAc DA response to heroin, and enhances the DA response to cocaine (15). Although blockade of classical MOP by naltrexone is not

sufficient to prevent METH self-administration (52). Recent evidence has demonstrated that co-activation of NOP and MOP receptors is essential for buprenorphine to reduce cocaine intake (14). Through coactivation of NOP and MOP receptors, bifunctional NOP/MOP receptor agonists can attenuate opioids and other abused drugs (53).Thus, buprenorphine regulates METH consumption through its unique and complex pharmacological effects.

N/OFQ and its NOP receptors expressed in the medial prefrontal cortex, VTA, and NAc exert a number of functional effects, including blocking stress-induced analgesia, anxiolytic-like effects, and reducing drug rewards (54). Accordingly, N/OFQ mRNA is expressed largely on GABA neurons, whereas NOP receptor mRNA is located on DA neurons. N/OFQ is in a position to influence DA neuronal activity by means of the NOP located on DA neurons (55). Moreover, intraventricular injection with N/OFQ or NOP receptor agonists significantly reduces alcohol intake and alcohol self-administration (56). N/OFQ blocks cocaine CPP (26) and maladaptive behavioral changes induced by repeated cocaine treatment (25) or rewarding properties of morphine and psychostimulants (27, 41). Buprenorphine has dual effects as an opioid receptor ligand; higher doses reduce ethanol consumption via the activation of NOR receptors (20). To elucidate this inhibitory mechanism, we performed pharmacological studies using the NOP antagonists thienorphine and SB-612111. SB-612111 behaves *in vivo* as a potent and selective NOP antagonist (32). Thienorphine, a novel analog of buprenorphine, can bind NOP but results in inactive stimulation, thereby antagonizing NOP (31). In the present study, neither thienorphine nor SB-612111 alone changed METH self-administration, indicating that the endogenous NOP system was not involved in the METH reinforcement behavior. However, their combined treatment with buprenorphine reversed the inhibition of METH reinforcement by buprenorphine, suggesting that the inhibition of METH reinforcement by buprenorphine may be mediated mainly through the activation of NOP receptor.

Buprenorphine treatment inhibited context or METH priming-induced METH-seeking behavior. However, it failed to affect the conditioned cues induced drug-seeking behavior. These results are similar to those of a previous report that buprenorphine reduces cocaine-seeking during extinction and following acute cocaine priming injections, but has no effect on stress-induced reinstatement (16). The exact mechanism by which buprenorphine modulates context or drug priming-induced drug-seeking behavior is not yet clear. First, the different circuits and mechanisms underlying relapse induced by contextual cues, conditioned cues, or drug priming are considered (57, 58). For example, a series of projections, primarily involving dopamine from the VTA to the NAc shell and glutamate from the BLA or dmPFC to the NAc core, appear to be the primary pathways mediating conditioned cue-induced reinstatement (59). The dmPFC projections to the NAc core and dopamine innervations of the vmPFC and NAc shell are likely involved in drug-primed reinstatement (60). The dorsal hippocampus and NAc shell play a significant role in the contextual reinstatement of drug seeking (61). The contextual cue-induced heroin relapse behavior may be the result of involvement of the hippocampal-NAc glutamate pathway and the VTA-NAc DA pathway (62). Buprenorphine enhances basal levels of DA (15) and increased basal levels of glutamate in drug-naïve and cocaine-exposed rats (17), which may facilitate CS salience. This possibility is further supported by data showing that naltrexone reduces the reinstatement of drug seeking induced by METH-associated cues (52, 63). Thus, the discrepant effects of buprenorphine on drug-seeking behavior induced by contextual cues and conditional cues may be related to the different mechanisms.

Another explanation is that buprenorphine may activate NOP to reduce DA release and inhibit contextual cue or drug priming-induced seeking behavior. Thus, N/OFQ administration prevents the reinstatement of ethanol-seeking behavior elicited by contextual cues (56). The present results showed that a NOP antagonist could reverse the inhibitory action of buprenorphine on METH priming drug-seeking behavior, which is consistent with previous reports. For example, genetic deletion of NOP receptors decreases heroin, cocaine, or alcohol self-administration and CPP (64) and potent and selective activation of NOP receptors is sufficient to decrease cocaine intake and seeking behavior in rats (65). These findings support the notion that low-dose buprenorphine is a weak dopamine releaser relative to heroin and METH, and that buprenorphine pretreatment can block the dopamine-releasing effects of heroin and METH (66).

Opioid receptor agonists can modulate the activity of dopamine neurons and can therefore modify the pharmacodynamic effects of METH on the dopaminergic system. The efficacy of adjunctive medication with buprenorphine has been demonstrated in the treatment of cocaine addiction, extending beyond opiate addiction. A few clinical trials have shown that buprenorphine maintenance decreases craving for METH in METH users (11, 12). Based on the efficacy of buprenorphine on heroin dependence, this study offers supporting evidence that buprenorphine may be used for the treatment of METH dependence. We systematically observed and analyzed the effects of buprenorphine on METH intake and relapse behaviors and found that buprenorphine has an inhibitory effect on METH self-administration, reward motivation, and drug-seeking behavior induced by drug priming. Meanwhile, it is cautious to clinical trials of buprenorphine for METH use disorder because buprenorphine may slightly stimulate the drug seeking induced by cues. Interestingly, naltrexone reduces the reinstatement of drug seeking induced by conditioned cues, on the other hand, it fails to affect the reinstatement induced by METH-priming (52, 63). Moreover, low doses of risperidone also can inhibit

the drug seeking induced by conditioned cues (67, 68).Thus, it will be beneficial to use buprenorphine in conjunction with other medicines such as naltrexone or risperidone to block the drug-seeking behavior induced by cues and drug priming.

Taken together, our results demonstrated that buprenorphine has a significant inhibitory effect on key aspects of METH dependence. Therefore, the present results suggested that buprenorphine can be used as an adjunctive therapy for the METH use disorders and relapse prevention.

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/s.

Ethics statement

The animal study was reviewed and approved by Ethics Committee of the Laboratory Animal Use and Care of Ningbo University.

Author contributions

FW, WS, and YC performed the experiments, analyzed the data, and wrote the manuscript. XZ, HD, and ML performed the experiments. HL was responsible for the study concept and supervised the experiments. EK and WZ was responsible for study design and critically revised the manuscript. All authors critically reviewed content and approved final version for publication.

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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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Associations of executive function and age of first use of methamphetamine with methamphetamine relapse

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Background and aims: Methamphetamine (MA) is a psychostimulant associated with a high relapse rate among patients with MA use disorder (MUD). Long-term use of MA is associated with mental disorders, executive dysfunction, aggressive behaviors, and impulsivity among patients with MUD. However, identifying which factors may be more closely associated with relapse has not been investigated. Thus, we aimed to investigate the psychological factors and the history of MA use that may influence MA relapse.

Methods: This cross-sectional study included 168 male MUD patients (MUD group) and 65 healthy male residents (control group). Each patient was evaluated with self-report measures of executive dysfunction, psychopathological symptoms, impulsiveness, aggressiveness, and history of MA use. Data were analyzed with *t*-tests, analyses of variance, and correlation and regression analyses.

Results: The MUD group reported greater executive dysfunction, psychopathological symptoms, impulsivity, and aggression than the control group. Lower age of first MA use was associated both with having relapsed one or more times and with having relapsed two or more times; greater executive dysfunction was associated only with having relapsed two or more times.

Conclusion: Patients with MUD reported worse executive function and mental health. Current results also suggest that lower age of first MA use may influence relapse rate in general, while executive dysfunction may influence repeated relapse in particular. The present results add to the literature concerning factors that may increase the risk of relapse in individuals with MUD.

KEYWORDS

methamphetamine use disorder, executive function, mental disorders, the age of first use, relapse

Introduction

Addiction to amphetamine-type stimulants is a global public health issue. According to the World Drug Report 2022 (1), methamphetamine (MA) is commonly used substance among amphetamine-type stimulants and widely used drug in China. By the end of 2021, China had about 0.79 million MA users, accounting for 53.4% of the total number of drug use disorders (2). MA use disorders (MUDs) is equivalent to the DSM-5 term of amphetamine-type substance use disorder that is a subtype of stimulant use disorders (3). MUD is any form of chronic and problematic MA use including abuse, misuse, dependence and use disorder regarding MA (4).

Studies have suggested that MA is highly addictive with a high relapse rate (5). However, there is a lack of effective methods to detect and reduce the likelihood of relapse.

Studies have observed an increased likelihood of mental disorders and cognitive impairment among individuals who use MA (6), with estimates that between 40 and 60% of users are thus affected (7, 8). The mental disorder symptoms include depression, anxiety, irritability, violent behavior, hallucinations, and delusions (9–11), while cognitive impairment includes deficits in learning, memory, attention, decision-making, social cognition, executive function, and working memory (12, 13). Such symptoms often produce progressive social and occupational deterioration as well as poor treatment outcomes, and some of these psychological indicators are closely related to relapse. For example, it has been found that treating depression and anxiety plays a vital role in preventing relapse in MUD patients (14). Impulsive behavior has been associated with the severity of MA addiction, and it can be used to predict MUD patients' quality of life following treatment (15). MA-induced aggressive behavior has also been associated with MUD relapse (10).

According to the research, executive function plays a crucial role in the prognosis of treatment efficacy and in preventing relapse in addiction, suggesting that improvement of MUD patients' executive function may enhance the effectiveness of their treatment (16). Executive function is an umbrella term that includes cognitive processes such as decision-making, impulse control, inhibitory control, behavioral flexibility, and working memory. Good executive function can identify and effectively control impulsive and compulsive drug-seeking behavior, thereby reducing the likelihood of relapse (17). Therefore, we suspected that executive dysfunction and related factors, including psychopathological symptoms, impulsivity, and aggression, may play a role in MA relapse.

Based on previous findings, the present study compared adult patients with MUD to healthy adults with no history of MA use in relation to executive dysfunction, psychopathological symptoms, impulsiveness, and aggressiveness. In an attempt to expand on the literature, the present study also aimed to investigate the psychological factors and the history of MA use that may influence MA relapse. Specifically, a key aim of the current study was to try to identify which factors (e.g., psychopathological symptoms, impulsive/aggressive traits, and MA usage characteristics) may be more closely associated with MA relapse.

Materials and methods

Subjects

A cross-sectional design was used in the current study. Male MUD patients ($n = 168$) were recruited from Bengbu Compulsory Isolated Drug Rehabilitation Center from July 2019 to March 2021. All participants met DSM-5 criteria for stimulant use disorder (methamphetamine-type), which will be referred to as MUD in this report. The diagnosis was confirmed by an associate professor psychiatrist. Inclusion criteria: (1) between 18 and 45 years old; (2) normal vision and hearing; (3) more than 6 years of education, i.e., primary school level or above; (4) participation in MA withdrawal treatment for <3 months; (5) no other substance use disorder (e.g., opioids, cocaine, or alcohol, except for cigarettes) in the past 5 years. Exclusion criteria: (1) mental disorders or neurological diseases (e.g., schizophrenia, mood disorder, stroke, epilepsy, or Parkinson's disease); (2) other chronic diseases (e.g., diabetes, hypertension, hyperlipidemia, and gastrointestinal diseases); (3) using any medication which may affect cognitive and executive function.

The staff members of the Bengbu Mental Health Center and the people in the local community were chosen as the control group (65 healthy adults), and none of them had a history of illicit drug use. The control parameters, such as gender, age, and education, matched the MA groups. All participants had to sign an informed consent form as a protocol. The study was approved by the Institutional Review Board (permission number: 2017-53) of Bengbu Medical University. All experiments were carried out following the approved guidelines and regulations.

Tools

Demographic questionnaire

This was used to collect the demographic information of the MA and Control groups, including age, years of education, and marital status.

Drug use questionnaire

Information on drug use by MUD patients was collected, including the age of first MA use (years), total duration of MA use (months), MA use before abstinence (g/occasion), and

the number of relapses (times). The number of relapses was represented by the number of times MUD patients entered the Compulsory Isolated Drug Rehabilitation Center.

Behavior rating inventory of executive function-adult version (BRIEF-A)

The BRIEF-A is a clinically validated questionnaire of executive function consisting of nine subscales (Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organization of Materials) tapping into various aspects of executive functioning in daily life (18). The BRIEF-A total score (an overall score that summarizes the nine subscales) is known as the Global Executive Composite (GEC). The BRIEF-A has 75 items on a three-point scale. Higher scores denote more impaired executive function. In this study, internal consistency of Cronbach's α of the questionnaire was 0.956, indicating that the scale had good reliability.

Self-report symptom inventory, symptom checklist 90 (SCL-90)

The SCL-90 (19) is a 90-item, five-point scale inventory used to evaluate psychopathological symptoms. The SCL-90 measures nine symptom domains of psychological distress: somatization, obsessive compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and "additional items." This study includes 10 subscales and the Global Severity Index (GSI). Cronbach's α of the questionnaire measured internal consistency was 0.907, and internal consistency by Cronbach's α of subscales was 0.716–0.857, indicating that the scale had good reliability.

Barratt impulsiveness scale 11 (BIS-11)

The BIS-11 (20) is used to evaluate the impulsive characteristics of individuals. The BIS-11 has 30 items spanning three dimensions: attentive impulse, motor impulse, and non-planning impulse. Each item is scored with a five-point scale. Higher scores reflect higher impulsivity and hyperactivity, inattention, and lack of planning. In this study, internal consistency was measured by Cronbach's α of the questionnaire was 0.887, indicating that the scale had good reliability.

Chinese version of buss-perry aggression questionnaire (AQ-CV)

The AQ-CV (21) is used to evaluate the aggressiveness of the subjects. The AQ-CV has 30 items assessing five dimensions of aggression: Physical Aggression, Verbal Aggression, Anger, Hostility, and Self-Aggression. Each item is scored with a five-point scale. A higher total score reflects higher aggression and aggressive traits. In this study, internal consistency measured by Cronbach's α of the questionnaire was 0.907, indicating that the scale had good reliability.

Statistical analysis

The SPSS 25.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis in this study. The measured data were expressed as (mean ± standard deviation, M ± SD), and the independent sample t-test was used to compare two groups of measured data. 2-Sample t-test, $\alpha = 0.05$, power values > 0.8, the sample size was calculated and compared with the actual sample size, if the calculated sample size was lower than the actual sample size, it passed the power analysis. Power calculations were conducted using minitab using a type 1 error rate (α) = 0.05, power ($1 - \beta$) = 0.80, effect size: Cohen's d (Cohen's $d > 0.5$, medium), which recommended a total sample size of N = 300 (MA group:216; Control group: 84). One-way Analysis of Variance (ANOVA) or Fisher's exact tests with Bonferroni *post-hoc* measured data for multiple groups, making multiple comparisons. Also, Spearman correlation analyses were used to identify the relationships between information on MA use and psychological characteristics. To correct for multiple comparisons, a p-value of 0.05/21 = 0.0024 was deemed significant. Ordinal regressions were used to assess the demographic information and psychological scale scores of MUD patients with varying the number of relapses. Binary logistic regression analysis was used to construct the prediction model equation of MA relapse. Discrimination and calibration of prediction models were tested using the receiver operating characteristic (ROC) curve test and the Hosmer-Lemeshow test. P-values < 0.05 (two-sided tests) were considered statistically significant.

Results

Demographics, MA use history in MA group and control group

There was no significant difference in age, education years, and marital status between the MA and Control groups ($P > 0.05$). In the MA group, first MA use was at 25.77 ± 7.44 years, total duration of MA use was 118.58 ± 72.22 months, MA use before abstinence was 0.49 ± 0.38 g/occasion, and the number of relapses was 2.13 ± 0.99 times (see Table 1).

Comparison of psychological characteristics between the MA and control groups

Independent-sample t-tests were used to compare the BRIEF-A, BIS-11, and AQ-CV total scores and the SCL-90

TABLE 1 Demographics and history of MA use in the MA group and control group.

	MA group ($n = 168$)	Control group ($n = 65$)	t/x^2	P
Age (years)	34.27 ± 6.60	34.15 ± 6.32	0.126	0.900
Education year (years)	6.94 ± 2.88	7.55 ± 2.70	−1.741	0.143
Marital status				
Married (%)	92 (54.76%)	36 (55.39%)		
Unmarried (%)	38 (22.62%)	14 (21.54%)	0.034	0.984
Divorced (%)	38 (22.62%)	15 (23.07%)		
Widowed (%)	0	0		
The age of first MA use (years)	25.77 ± 7.44			
Total duration of MA use (months)	118.58 ± 72.22			
MA use before abstinence (g/occasion)	0.49 ± 0.38			
Number of relapses (times)	1.54 ± 0.27			

Data accord with normal distribution were given as mean ± standard deviation (M ± SD).
MUD, methamphetamine use disorder.

TABLE 2 Comparison of psychological characteristics between the MA group and control group.

Variable	MA group ($n = 168$)	Control group ($n = 65$)	t	P
GEC (BRIEF-A total score)	106.92 ± 23.54	97.91 ± 25.04	2.575	0.011*
SCL-90				
Somatization	21.79 ± 8.05	15.26 ± 5.72	6.846	0.000***
Obsessive compulsion	20.75 ± 7.03	20.35 ± 5.79	0.407	0.685
Interpersonal sensitivity	15.79 ± 5.82	15.86 ± 6.34	−0.079	0.937
Depression	23.66 ± 8.72	20.57 ± 8.09	2.459	0.015*
Anxiety	17.32 ± 6.68	15.11 ± 6.11	2.305	0.022*
Hostility	10.70 ± 4.64	8.72 ± 3.26	3.127	0.002**
Phobic anxiety	9.72 ± 3.51	10.12 ± 3.92	−0.759	0.448
Paranoid ideation	9.76 ± 3.74	9.00 ± 3.24	1.434	0.153
Psychoticism	16.40 ± 6.08	15.23 ± 5.86	1.324	0.187
Additional items	12.92 ± 4.35	10.06 ± 3.90	4.602	0.000***
GSI (SCL-90 total score)	158.66 ± 50.94	158.66 ± 46.71	2.525	0.012*
BIS-11 total score	44.57 ± 15.08	37.45 ± 12.27	3.395	0.001**
AQ-CV total score	37.52 ± 17.63	27.33 ± 14.30	4.558	0.000***

Data accord with normal distribution were given as mean ± standard deviation (M ± SD).
BRIEF-A, Behavior Rating Inventory for Executive Function of adult version; SCL-90, Self-report symptom inventory, Symptom checklist 90; GEC, Global Executive Composite; GSI, Global Severity Index; BIS-11, Barratt Impulsiveness Scale-11; AQ-CV, Chinese version of Buss-Perry aggression questionnaire.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

subscale scores between the MA and control groups. MUD patients reported greater executive dysfunction, impulsiveness, aggressiveness, and psychopathological symptoms relative to the control group (see Table 2). All the variables with significant differences passed the power analysis.

Relationship between MA use history and psychological characteristics of MUD patients

Spearman correlation analyses were used to identify the relationships between the information on MA use history and psychological characteristics in the MA group.

After Bonferroni's corrections, there's a correlation between number of relapses and the age of first MA use, between age and the age of first MA use, between age and total duration of MA use. None of the other scores and sub-scales showed statistically significant correlations ($P > 0.0023$; see Table 3).

Comparison of demographic information and psychological characteristics in MUD patients with different number of relapses

The demographic information and psychological assessment scores of MUD patients with varying the number of relapses were compared. The age of first MA use, total duration of MA, phobic anxiety, AQ-CV total score, BIS-11 total score, and GEC were significantly different with different number of relapses ($P < 0.05$), based on one-way ANOVA or Fisher's exact tests with Bonferroni *post-hoc* analysis, as shown in Table 4.

Test level after correction for multiple comparisons is $P = 0.05/3 = 0.017$. Only the age of first MA use and first MA use occurred at 19 years old or younger were significantly different with different number of relapses ($P < 0.017$).

The influencing factors of the number of relapses were identified using ordinal regression analysis

In order to conduct an ordinal regression analysis, the variables ($P < 0.05$) in Table 4 were used as independent variables and the number of relapses as dependent variables. The results showed that the age of first MA use, the total scores of BRIEF-A (GEC), and BIS-11 entered the regression equation (see Table 5). The parallel line test $P = 0.124 > 0.05$ indicates no multicollinearity between variables of the regression equation.

TABLE 3 Relationship between MA use history and psychological characteristics of MUD patients.

Variable	Number of relapses (times)	The age of first MA use (years)	Total duration of MA use (months)	MA use before abstinence (g/occasion)
	r	*r*	*r*	*r*
Age (years)	0.118	0.694***	0.303***	0.012
Marital status	0.073	−0.193*	0.114	0.104
Education year (years)	0.080	−0.215**	0.009	0.023
Number of relapses (times)	1	−0.274***	0.187*	0.118
The age of first MA use (years)	−0.274***	1	−0.224**	−0.219**
Total duration of MA use (months)	0.187*	−0.224**	1	0.212**
MA use before abstinence (g/occasion)	0.118	−0.219**	0.212**	1
GEC (BRIEF-A total score)	0.225**	−0.075	0.106	0.098
SCL-90				
Somatization	0.015	0.003	0.140	−0.013
Obsessive compulsion	0.007	0.041	0.083	0.007
Interpersonal sensitivity	0.059	0.029	0.070	−0.009
Depression	0.007	0.093	0.116	−0.062
Anxiety	0.004	0.127	0.038	−0.026
Hostility	0.071	0.014	0.017	0.019
Phobic anxiety	0.059	−0.016	0.020	0.104
Paranoid ideation	0.190*	0.026	0.035	−0.014
Psychoticism	0.037	0.121	0.091	−0.067
Additional items	0.075	0.039	0.047	−0.051
GSI (SCL-90 total score)	0.034	0.058	0.098	−0.010
BIS-11 total score	0.155*	−0.153*	0.083	0.111
AQ-CV total score	0.148	−0.076	0.118	0.077

MUD, methamphetamine use disorder; BRIEF-A, Behavior Rating Inventory for Executive Function of adult version; BIS-11, Barratt Impulsiveness Scale-11; GEC, Global Executive Composite; GSI, Global Severity Index; SCL-90, Self-report symptom inventory; AQ-CV, Chinese version of Buss-Perry aggression questionnaire.
*$P < 0.05$, **$P < 0.01$, Bonferroni's corrections, ***$P < 0.05/21 = 0.0023$.

Construction of prediction model for MA relapse by binary logistics regression analysis

Among 168 MUD patients, 46 patients had never relapsed (zero relapse), 73 patients had relapsed one time (one relapse), and 49 patients had relapsed two or more (≥ two relapses). Considering (1) zero relapse (46 patients) and ≥ one relapse (122 patients) and (2) ≤ one relapse (119 patients) and ≥ two relapses (49 patients) as the dependent variables and the age of first MA use, BIS-11 total score, and BRIEF-A total score (GEC) as the independent variables, binary logistic regression analyses were conducted to construct the two relapse prediction model equations (see Table 6). The two prediction model equations showed that the age of first MA use was a significant predictor of ≥ one relapse and ≥ two relapses; GEC (executive dysfunction) was a significant predictor of ≥ two relapses; and BIS-11 total score was not a significant predictor in either relapse prediction model.

Discussion

Current results indicated that MUD patients had greater executive dysfunction, psychopathological symptoms, impulsiveness, and aggressiveness than healthy controls. Previous studies also found that MUD patients exhibit executive dysfunction, anxiety, depression, impulsive behavior, and aggressiveness (9, 10, 12, 22). Furthermore, in the current study, lower age of first MA use was associated both with having relapsed one or more times and with having relapsed two or more times, whereas greater executive dysfunction was associated only with having relapsed two or more times. Hence, current findings further suggest that lower age of first MA use may influence relapse rate in general, while greater executive dysfunction may influence higher rates of relapse in particular.

1. Executive dysfunction is associated with relapse.

Executive function is often viewed as a complex cognitive function that includes a series of functions such as inhibition,

TABLE 4 Comparison of demographic information and psychological characteristics in MUD patients with different number of relapses.

	Number of relapses					
	Zero[1] ($n = 46$)	Once[2] ($n = 73$)	Twice and more relapse[3] ($n = 49$)	F/x^2	P	*Post-hoc*
Age (years)	33.23 ± 7.80	34.23 ± 5.74	35.12 ± 6.48	0.955	0.387	
Education year (years)	6.89 ± 3.72	6.59 ± 2.33	7.51 ± 2.63	1.392	0.251	
Marital status	1.52 ± 0.69	1.73 ± 0.85	1.87 ± 0.94	1.569	0.199	
The age of first MA use (years)	28.5 ± 8.73	25.52 ± 5.73	23.15 ± 7.07	6.570	0.002**	1>2, 1>3
First MA use occurred at 19 years old or younger (%)	6 (13.04)	12 (16.43)	22 (44.89)	17.138	0.000**	3>2, 3>1
Total duration of MA use (months)	102.23 ± 74.68	114.48 ± 65.80	140.94 ± 75.33	3.661	0.028*	1<3, 2<3
MA use before abstinence (g/occasion)	0.48 ± 0.32	0.43 ± 0.43	0.58 ± 0.32	2.199	0.114	
GEC (BRIEF-A total score)	104.9 ± 21.88	103.85 ± 22.55	114.85 ± 25.65	3.857	0.023*	1<3, 2<3
SCL-90						
Somatization	22.16 ± 8.70	21.46 ± 7.56	21.93 ± 8.26	0.116	0.891	
Obsessive compulsion	21.50 ± 6.30	20.25 ± 7.26	20.80 ± 7.41	0.379	0.685	
Interpersonal sensitivity	16.16 ± 5.6	15.28 ± 5.84	16.21 ± 5.10	0.548	0.579	
Depression	24.80 ± 8.93	22.94 ± 8.6	23.65 ± 8.19	0.728	0.485	
Anxiety	18.68 ± 7.69	16.29 ± 6.18	17.57 ± 6.25	2.054	0.132	
Hostility	11.00 ± 4.80	9.94 ± 4.13	11.54 ± 5.11	1.697	0.187	
Phobic anxiety	9.86 ± 3.68	9.43 ± 3.03	10.00 ± 4.02	0.464	0.629	
Paranoid ideation	10.72 ± 4.43	8.99 ± 3.17	10.00 ± 3.66	3.079	0.049*	2<1
Psychoticism	17.07 ± 6.01	15.68 ± 6.03	16.84 ± 6.21	0.907	0.406	
Additional items	13.23 ± 4.79	12.42 ± 3.93	13.39 ± 4.51	1.021	0.363	
GSI (SCL-90 total score)	162.98 ± 51.59	154.18 ± 50.23	160.88 ± 42.75	0.541	0.583	
BIS-11 total score	43.58 ± 13.29	41.80 ± 14.79	48.62 ± 15.33	3.654	0.028*	2<3
AQ-CV total score	38.04 ± 15.86	33.96 ± 16.68	42.91 ± 19.62	3.421	0.035*	2<3

One-way ANOVA or Fisher's exact tests with Bonferroni *post-hoc* analysis, test level after correction for multiple comparisons is $P = 0.05/3 = 0.017$. Only the age of first MA use were significantly different with different number of relapses ($P < 0.017$). *$P < 0.05$; **$P < 0.017$.
MUD, methamphetamine use disorder; BRIEF-A, Behavior Rating Inventory for Executive Function of adult version; GEC, Global Executive Composite; SCL-90, Self-report symptom inventory, Symptom checklist 90; GSI, Global Severity Index; BIS-11, Barratt Impulsiveness Scale-11; AQ-CV, Chinese version of Buss-Perry aggression questionnaire.

working memory, planning, impulse control, mental flexibility, and initiating and monitoring actions (23). Specifically, the most important executive function factor related to relapse is inhibitory control (24). Drug addiction can be viewed as a transition from voluntary, recreational drug use in the early stages to habitual and compulsive drug-seeking in the later stages (25, 26). Habitual drug use was the basis of compulsive drug-seeking. In habitual phase, when drugs are not available, addicts experience strong cravings, leading to the transformation of the habit into compulsive drug-seeking behaviors or relapse (27). Compulsive drug-seeking behaviors and relapse can be defined as the maladaptive persistence of response despite adverse consequences (28) and represents a loss of top-down inhibitory control (29, 30). Therefore, the essence of compulsive drug-seeking behavior and relapse is dysfunctional inhibitory control. Thus, there is a strong association between executive dysfunction and relapse.

2. The age of first MA use is associated with relapse.

Compared to adults diagnosed with MUD whose onset of MA use occurred in adulthood, adolescents (19 years of age or younger) diagnosed with MUD whose onset of MA use occurred in adolescence have displayed less cortical thickness in the prefrontal cortex, which was associated with worse performance on neuropsychological tests assessing executive function (31). This study also showed that the rate of first MA use occurred at 19 years old or younger was positively correlated with the number of relapse. In addition, an earlier onset of adolescent MA use has been related to more metabolic dysfunction in the anterior cingulate cortex and greater deficits in inhibitory control (32). Given that executive dysfunction (including inhibitory control deficits) may be a primary factor influencing drug relapse (12, 17, 33), these previous findings may help explain why age of first MA use and executive dysfunction were associated with MA relapse in the current study.

Furthermore, during adolescence, developmental changes occurring during the maturation of the nervous system lead to increased plasticity in the striatum, resulting in a high density of striatal dopamine receptors, and enhancing susceptibility to MA abuse (34, 35). MA is a drug that mainly acts on the dopamine system, increasing dopamine release to the striatum through mesolimbic pathways (36). Therefore, in adolescents, MA will cause higher levels of excitement and potential damage to the striatum than in adults. The striatum is closely linked to both MA addiction (37) and executive function (38). Therefore, we speculate that this may be one of the reasons why the earlier the age of first MA use, the greater the number of relapses.

However, some researchers suggest that MA has minor damage to cognitive function (39) and some studies even suggest that MA improves cognitive performance in selected domains (40). We suspect that this may be related to the dose and duration of MA use. For example, previous studies have found that short-term administration of MA at low doses can produce neuroprotective effects, but high doses or long-term MA can lead to neurotoxicity (41, 42). In the current study, the executive dysfunction in the MUD patient group that had relapsed once was similar to the executive dysfunction in the MUD patient group without a history of relapse (as shown in Table 4). Still, executive dysfunction in the current study was associated specifically with having relapsed two or more times, which suggests that executive dysfunction may play a role in repeated relapse and thus more chronic use of MA.

This study also found an interesting phenomenon, namely, spearman correlation analyses showed that a significant association between the age of first MA use and the total duration of MA use ($P < 0.01$), in other words, the earlier a person starts using MA, the longer they are likely to use it. In addition, it was also found that both the age of first MA use and the total duration of MA use were associated with the number of relapses ($P < 0.01$ and $P < 0.05$, respectively). However, regression analysis indicated that the total duration of MA use may be less associated with relapse than executive dysfunction and the age of first MA use. Possible reasons are as follows: (1) Relapse after withdrawal from MA use may cause more serious

TABLE 5 Using ordinal regression analysis to screen the influencing factors of the number of relapses.

Variable	Estimate	S.E	Wald	*P*	*VIF*
The age of first MA use (years)	−0.068	0.023	8.829	0.003**	1.083
Total duration of MA use (months)	0.003	0.002	2.140	0.143	1.063
Paranoid ideation	−0.009	0.013	0.412	0.521	1.616
AQ-CV Total score	0.013	0.012	1.223	0.269	1.815
BIS-11 total score	0.025	0.010	6.289	0.012*	2.203
GEC (BRIEF-A total score)	−0.163	0.059	7.701	0.006**	1.856

AQ-CV, Chinese version of Buss-Perry aggression questionnaire; BRIEF-A, Behavior Rating Inventory for Executive Function of adult version; GEC, Global Executive Composite; BIS-11, Barratt Impulsiveness Scale-11.
The parallel line test $P = 0.124 > 0.05$ indicates that there is no multicollinearity.
*$P < 0.05$, **$P < 0.01$.

TABLE 6 Construction of prediction model for MA relapse using binary logistic regression analysis.

Construction of relapse prediction model	Dependent variable	0 Relapse (46 patients) and ≥ once relapse (122 patients)				≤ Once relapse (119 patients) and ≥ twice relapse (49 patients)			
	Independent variable	The age of first MA use (years)	GEC	BIS-11 total score	Constant	The age of first MA use (years)	GEC	BIS-11 total score	Constant
	B	−0.070	0.009	−0.010	2.264	−0.069	0.027	−0.092	−1.267
	S.E	0.024	0.009	0.012	1.084	0.030	0.010	0.068	1.152
	Wald	8.435	0.916	0.755	4.361	5.184	6.921	1.837	1.209
	P	0.004**	0.339	0.385	0.037	0.023*	0.009**	0.175	0.272
	Exp(B)	0.932	1.009	0.990	9.624	0.934	1.028	0.912	0.282
	Relapse model	Equation one = 2.264–0.070* The age of first MA use				Equation two = −1.267–0.069* The age of first MA use + 0.027*GEC			
Discrimination	ROC curve	AUC = 0.650 95% CI (0.555–0.745) $P = 0.003$				AUC = 0.669 95% CI (0.577–0.761) $P = 0.001$			
Calibration	Hosmer-Lemeshow	$R^2 = 11.273$, $P = 0.187$				$R^2 = 12.091$, $P = 0.147$			

The prediction models of MA relapse were constructed by binary logistics regression analysis. The variable that predicts ≥ once relapse is age of first MA use. The variables that predicts ≥ two times relapse are age of first MA use and GEC. ROC curve tests and Hosmer-Lemeshow test demonstrated that the discrimination and calibration of two relapse model equations were all very high.
GEC, Global Executive Composite; BIS-11, Barratt Impulsiveness Scale-11; AUC, area under the curve; CI, confidence interval.
*$P < 0.05$, **$P < 0.01$.

nerve damage than continuous use of the MA. Studies have found that preconditioning with low doses of MA can reduce the neurotoxicity of large doses given later (41, 42). This suggests that relapse after long-term withdrawal may result in the same level of neurotoxicity and cognitive dysfunction as naive drug use, both of which are more serious than long-term continuous drug use. (2) The earlier a person takes drugs, the more likely they are to relapse. Previous studies have found that adolescents are at great risk of starting drug use and subsequent addiction (43). Early drug use, for example, in adolescence, is associated with a greater likelihood of transition from drug use to abuse, leading to dependence, a higher frequency of relapse throughout the life cycle, and a shorter time window from first use to the establishment of dependency (44).

To sum up, the above studies suggest that both the age of first MA use and executive dysfunction are more strongly correlated with the number of relapses than the total duration of MA use. Another reason may be the cross-sectional design which hinders the collection of temporal evidence.

Limitations

The current study has a number of limitations worth noting. First, this study used a cross-sectional design, which prevents establishing the temporal precedence of executive dysfunction and restricts the ability to make causal inferences. Although executive dysfunction may be secondary to chronic MA use, individuals with lower levels of preexisting executive function may also be more prone to develop and persist in the problematic use of MA. Second, the MUD group consisted of MUD patients in forced isolation as part of their treatment. This forced isolation may exert psychological stress on MUD patients, which might lead to detrimental changes in mental health and executive function. Consequently, this was a potential confounding factor in the present study. Third, because there were only male MUD patients in the Bengbu Compulsory Isolated Drug Rehabilitation Center, we could only recruit male participants for the present study. Therefore, current findings may not generalize to female MUD patients, and additional research including female MUD patients is needed. Fourth, the questionnaire-based (subjective) assessment of executive dysfunction may have been prone to subject and experimenter bias. Future research on MA relapse would benefit from administering more objective neuropsychological assessments, such as the Wisconsin Card Sorting Test (45), event-related potential (46), and eye tracking (47).

Fifth, we did not assess whether MUD was mild, moderate or severe. The severity of MUD was also a potential confounding factor affecting the results of data analysis. Lastly, the present study only included individuals who had been in treatment for <3 months, and prior research (48) has evidenced that MUD-induced cognitive control deficits may improve with long-term abstinence. Thus, executive dysfunction associated with different stages of MA abstinence remains unknown, justifying further investigation.

Conclusion

Current results evidenced that patients with MUD have worse executive function and mental health, consistent with prior research. Current findings further suggest that executive dysfunction and the age of first MA use may play important roles in MA relapse: More specifically, lower age of first MA use may influence relapse rate in general, while executive dysfunction may influence repeated relapse in particular. These findings add to the literature concerning factors that may increase the risk of relapse in individuals with MUD.

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 Institutional Review Board (permission number: 2017-53) of Bengbu Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

L-LM, L-JW, and D-LJ conceived and designed the experiments. X-CZ, H-JT, W-JW, P-PS, LZhu, YW, H-NL, WZ, Y-JW, and J-DL carried out experiments. LZhu, L-LX, XS, and X-CZ analyzed experimental data. W-YS contributed analysis tools. YW and H-SX wrote the first draft of the manuscript. D-LJ provided critical revision of the manuscript for important intellectual content. All authors have materially participated in the manuscript preparation. All authors contributed to the article and approved the submitted version.

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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.2022.971825/full#supplementary-material

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Promoting self-change in cannabis use disorder: Findings from a randomized trial

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Background: A growing body of literature supports the efficacy of cognitive-behavioral therapy (CBT) and motivational interviewing (MI) for the treatment of problematic cannabis use, diagnostically referred to as cannabis use disorder, though most individuals do not access formal treatment. Stepped-care-type models emphasize interventions across a continuum of severity and there is a need for more treatment options across this continuum. This project focused on the evaluation of the least intensive of the individual interventions – promotion of self-directed recovery.

Methods: Using a three-arm randomized control trial design, adults (N = 186) with problematic cannabis use and who wished to recover with minimal professional support were recruited from across Canada and randomized to receive a self-directed treatment workbook based on CBT and MI principles (WB; n = 61), the workbook plus a single MI session (WMI; n = 61) or a delayed treatment control (DT; n = 65) condition. Participants completed 3-month and 6-month follow-up assessments.

Results: Across conditions, GEE modeling revealed that the baseline to 3-month slopes differed significantly from zero, $ps < 0.001$. Participants in the WMI condition reduced their frequency of use to a greater extent than the WB alone, $p = 0.005$, and DT groups, $p = 0.02$. Chi-square analysis revealed that participants in the WMI condition also showed greater rates of abstinence at 3-months follow-up than participants in the WB or DT condition, $p = 0.046$. Changes in the frequency of cannabis use between 3-months and 6-months did not differ significantly between groups, $ps > 0.05$. For quantity of cannabis use, a significant effect of time emerged, $p = 0.002$. However, no between-group effects were significant from baseline to 3-months, or from 3- to 6-months, $ps \geq 0.06$.

Conclusion: Overall, results support the utility of a brief self-directed workbook in combination with a single MI session at promoting changes in cannabis use. This self-directed intervention has the potential to fill an important need in that the self-directed intervention can attract individuals who wish to recover with minimal professional support.

Clinical trial registration: [https://www.isrctn.com/], identifier [ISRCTN42632893].

KEYWORDS

cannabis, marijuana, cognitive-behavioral therapy, motivational interviewing, self-directed intervention, treatment

Introduction

In 2018, the Canadian federal Cannabis Act legalized recreational cannabis distribution and use, with a key objective of protecting public health (1). The ease of accessibility of cannabis and normalization of its use due to legalization have raised significant concerns regarding potential increases in heavy use and, consequentially, problematic cannabis use and its associated harms (2). Problematic use is diagnostically referred to as cannabis use disorder (CUD) and ranges from mild to moderate to severe (3). A successful public health approach to non-medical cannabis use, in addition to prevention and consumer protection, must also include a range of intervention options for individuals with problematic cannabis use (4). Stepped-care-type models contribute effectively to a public health approach. They emphasize interventions across a continuum of severity, ranging from public awareness messages to encourage responsible use and readiness to change to intensive inpatient or outpatient treatment services for individuals with severe problems (5, 6). This project focuses on evaluation of the least intensive of the individual interventions - promotion of self-recovery, commonly referred to as self-directed change.

Paradoxically, despite low rates of treatment-seeking among people with CUD, the demand for treatment is increasing across the globe. Cannabis is the most frequent psychoactive substance reported by treatment-seekers in North America, Central and South America, Africa, European Union countries, and Australia (7). This is likely due, in part, to increases in the frequency of use, the number of people with cannabis use disorder, and increased awareness of problems associated with cannabis use. The potency of cannabis products has also increased dramatically in the past decade (8), which could arguably contribute to the increased rates of CUD, although this relationship has not yet been established.

Fortunately, a growing body of literature supports the efficacy of several psychological interventions for cannabis problems. The utility of two complementary treatment models, cognitive-behavioral therapy (CBT) and motivational enhancement therapy [MET; (9–11)] have been investigated and shown to be efficacious for the treatment of CUD by groups of independent researchers (9–14). CBT models help clients to understand the contingencies of substance misuse, and to develop relapse prevention and coping skills (15). Common techniques include learning what situations, people, and objects can trigger cravings or a desire to use, increasing awareness of thinking patterns that contribute to continued cannabis use, and identifying high-risk situations. MET is based on Motivational Interviewing (MI) principles and seeks to enhance motivation to change substance use behavior by providing non-judgmental feedback, resolving ambivalence, and via goal setting (15).

Evidence suggests that a combination of CBT and MET is most efficacious for CUD (9, 16, 17). The Marijuana Treatment Project [MTP; (18)] examined the efficacy of a CBT/MET treatment across three demographically diverse treatment sites; adults with CUD were randomized to receive a 2-session MET intervention, a 9-session MET plus CBT and case management intervention, or a delayed treatment control. At 15-months follow-up, individuals in both active interventions showed greater reductions in cannabis use and problems relative to the control condition. Additionally, individuals in the MET plus CBT and case management intervention demonstrated the greatest reductions in the frequency of cannabis use and symptoms of addiction (18). Similarly, the CANDIS treatment program (19, 20) examined the efficacy of a 10 session CBT/MET plus problem solving treatment program in Germany. Adults with CUD who received 10 sessions of CBT/MET plus problem solving showed greater rates of abstinence, reduced frequency of cannabis use, and reduced cannabis-related problems compared to adults in the waitlist control. Most of these gains were maintained at six-months (19). The Cannabis Youth Treatment [CTY; (11)] study also found a 5-session MET plus CBT intervention to be as effective as other more intensive and costly treatments. In sum, MET

plus CBT is an effective treatment for CUD among treatment-seeking individuals.

Although the literature supports the efficacy of CBT + MET in the treatment of CUD, relatively few individuals will seek available treatments. The most frequently cited reasons that many individuals are not willing to seek treatment are embarrassment (i.e., stigma) and a desire to "do it on their own" (21, 22). This latter reason supports the finding that the most common pathway to recovery for CUD and for other addictions is recovery without treatment (23). A stepped-care approach may enhance the provision of treatment for CUD by providing individuals with the opportunity to choose a level of intervention that is consistent with their goals and preferences, such as self-directed change. Self-directed interventions also overcome many of the perceived limitations evident in formal treatment (i.e., availability, level of intensity). They support the desire to recover with minimal support and are also relatively inexpensive, accessible, and have reduced stigma compared to formal treatment. In this context, formal treatment refers to psychosocial treatment with a mental health professional, in an individual or group context or attendance at a mutual support group (such as a 12-step group). Several lines of research suggest that augmenting natural recovery with cognitive-behavioral and motivational tools can promote recovery in a larger population than is reached by formal treatment, and it may be preferable to many individuals. First, formal treatment is a limited resource, and such interventions are typically of interest to people with more severe problems. However, addiction severity falls on a continuum from mild to moderate to severe (3), and individuals with mild to moderate problems comprise a significant proportion of individuals with addictive disorders, including CUD (24). These individuals are also in need of support. Although many individuals with CUD will initiate a self-change process, they tend to have five to six years of problematic use before this occurs (21, 25). Moreover, few of these individuals with CUD will seek available treatment.

Second, brief interventions that facilitate self-change have demonstrated effectiveness with other addictive disorders (24, 26). These brief, self-directed interventions typically utilize self-directed written materials, worksheets, and provision of personalized feedback (24). For example, in our lab, we have developed a self-recovery program for problem gambling that involves a self-directed workbook with a motivational interview conducted via telephone (27–30). This treatment has been recognized as an evidence-based intervention by the US National Registry of Evidence-based Programs and has been adapted for use in a variety of countries (31) and seven languages, illustrating that it can be scaled for national accessibility. Several self-directed treatments have been developed for cannabis use in adults, though they have been largely limited to web-based approaches (32–34). One study by Rooke and colleagues (32) tested *Reduce Your Use*, a self-directed online treatment program among a sample of 225 individuals seeking to reduce or stop using cannabis. Participants were assigned to either the treatment program which consisted of modules based on cognitive, motivational, and behavioral principles or assigned to a cannabis information control condition. The intervention group showed significantly lower frequency of cannabis use at 3-months follow-up, but not lower quantity. In contrast, Sinadinovic and colleagues (33) found no benefit of an online treatment program with optional therapist communication via chat compared to a waitlist control group. Nevertheless, a recent meta-analysis of nine web-based interventions for prevention and treatment of CUD highlighted the potential utility of such interventions (35). As such, self-directed treatments for CUD appear promising. However, workbook-based treatments that have demonstrated utility with other addictive disorders have not been considered in the context of cannabis.

Third, research in our lab has demonstrated that recovery from CUD without treatment is common, and that individuals who recover without treatment experience (i.e., natural recovery) show similar change-processes to those who experience treatment-assisted recovery (25). In one study, we recruited individuals who had recovered from CUD (N = 119) with formal treatment or via natural recovery (25). Both groups showed remarkably similar motivators and processes of recovery. Individuals in both groups provided the same most cited motivations for reducing problematic cannabis use; Namely they reported that their use became inconsistent with their self-image and lifestyle, and that it led to perceived psychological problems. These results are consistent with other studies that have previously reported motivations in individuals who had sustained only short-term treatment goals at the time of the study (36–38), lending confidence to our findings. Additionally, individuals in both groups described utilizing the same cognitive strategies (e.g., considering the positive and negative consequences of cannabis use) and behavioral strategies (e.g., avoidance of high-risk situations) as part of the recovery process.

A second report that examined individual experiences to gain a richer understanding of the recovery process, showed that both groups most often attributed their recovery success to cognitive and motivational factors, consistent with the previous analyses (39). This pattern of change processes in CUD has also been demonstrated with other addictive disorders such as alcohol, other drugs, and gambling, and has fueled the development of brief interventions that facilitate self-change (24, 26). Most participants in both groups reported that they would recommend both formal treatment and self-help materials to another person experiencing concerns related to their cannabis use. However, treatment-assisted participants who had chosen moderation goals (i.e., to moderate their use versus quitting) were more likely to recommend natural recovery compared to those who had chosen abstinence goals. Given that most treatment programs emphasize abstinence (9),

rather than also supporting moderated use, there may be a lack of fit between personal moderated use goals and the abstinence goal imposed by treatment programs. This lack of fit may partly explain why treatment-assisted participants who had chosen moderation goals were less likely to recommend treatment-assisted recovery. Taken together, these findings highlight the perspective of individuals with CUD recovery experience, which is critical to planning effective interventions that individuals are likely to utilize (40).

In sum, research suggests that a hybrid approach of two complementary therapeutic models, CBT and MET is an effective treatment for CUD. However, many individuals are unable to receive formal treatment, due to limited availability, or are unwilling to seek treatment because of stigma or a desire for natural recovery. Fortunately, brief interventions that facilitate self-change are effective, and similar change processes are observed in both treatment-assisted and natural recovery. These change processes may be utilized to provide support to individuals through a brief self-directed intervention. An intervention that can attract individuals who wish to recover with minimal professional support would also bridge the current mismatch between current treatment needs and available services and fill an important role within an integrated public health approach.

The aim of the present research was to test the clinical utility of a brief self-directed intervention for individuals with problematic cannabis use who wished to recover with minimal professional support. The main objectives were to determine whether a self-directed workbook package could produce significant change in cannabis use among individuals with problems associated with cannabis use in the short-term (up to 6-months), and the benefit of brief motivational interviewing in combination with the self-directed treatment. To this end, a three-arm randomized control trial (RCT) design was utilized, and participants were randomly assigned to (i) receive the self-directed workbook alone (WB); (ii) receive a brief motivational interview in addition to the workbook (WMI); or to a delayed workbook treatment control condition (DT). We had three primary *a priori* hypotheses:

(1). Participants in the WMI and WB groups would show significantly lower frequency and quantity of cannabis use at 3-months follow-up than those assigned to the DT group, as individuals in the DT group would have not yet received the workbook.

(2). Participants in the WMI and WB groups would show greater significantly greater rate of change in their frequency and quantity of cannabis use than those in the DT group. This difference was expected to be most pronounced between baseline and 3-months, versus between 3-month and 6-months follow-up. Between 3- and 6-months, it was predicted that the rate of change for participants in the WMI and WB groups would slow, having already made significant gains, whereas participants in the DT group would show an increased rate of change, having received the workbook at 3-months.

(3). Participants who received a motivational interview (WMI condition) would show greater reduction in the frequency and quantity of cannabis use than participants who received the workbook alone (WB condition) or participants in the DT condition.

Materials and methods

Study design

The current study utilized a three-arm randomized control trial that compared the efficacy of a self-directed treatment workbook alone and in combination with a brief motivational intervention in its ability to reduce problematic cannabis use and associated problems. The two intervention groups were compared against each other and against a wait list control group in which participants received a baseline assessment and access to the workbook following a three-month waiting period. Participants completed a follow-up assessment three months and six months after the baseline assessment.

Following completion of the baseline assessment, participants were assigned to one of three groups, stratified by gender and probl em severity (CUDIT-R $\leq$22 or $\geq$23): (i) workbook plus motivational interview (WMI); (ii) workbook only (WO); or (iii) delayed workbook treatment control (DT). The *blockrand* package (41) in R version 4.0.3 (42) was used to create stratified random assignments within randomly chosen block sizes of 3, 6, 9, and 12. This procedure allows for relatively equal sample sizes across groups without selection bias (43).

Recruitment procedures

Adapting earlier procedures (30), online media announcements across various platforms were used to recruit Canadian residents who were concerned about their cannabis use and who were interested in self-directed change. To mitigate risk of participants misreporting symptoms to be eligible for studies with explicit inclusion criteria, a two-stage screening process was utilized (44, 45). Participants were first directed to Qualtrics and asked to complete a brief screening survey. Attempted survey completions from a Virtual Private Server were automatically detected and blocked to ensure that participants completing the survey were in Canada at the time. IP addresses were automatically and manually checked for duplicate response attempts.

Eligibility criteria were adapted from a previous brief intervention for CUD (12) and previous research in our lab on self-change interventions (28): (a) 18 years of age or older; fluent in English; (b) perception of a cannabis use problem; (c) a score

of *13* or greater on the Cannabis Use Disorders Identification Test-Revised [CUDIT-R; (46)]; (d) had used cannabis at least once in the past month; and (e) not currently receiving any other treatment for cannabis use problems (including 12-step programs and any medical or psychological treatment where cannabis problems are addressed). Participants were not excluded from the study based on engagement in other potentially addictive substances or behaviors, though this was assessed at baseline.

Interested participants who met the eligibility criteria outlined above were invited to complete the baseline assessment where these criteria were confirmed. Additional eligibility criteria included: (f) consistent responding, characterized by scores on the CUDIT-R that did not differ by more than three points from the score received at screening; and (g) provision of a valid Canadian address where the workbook could be mailed.

Sample justification

We aimed to recruit a sample of 120 participants (40 per group). We estimated [based on (28)], that we would successfully follow at least 102 at 3-months and 90 and 6-months. *A priori* power calculations were conducted for a clinical superiority trial with continuous outcome variables. Based upon estimated baseline scores on the primary outcome variable (days of cannabis use), this sample would be able to show statistically significant baseline to follow-up effects with power = 0.90; For days of use in past month, assuming a baseline mean of 25.38 (SD = 6.2; Stephens et al. (14), and a reduction to 17.09 days in the delayed workbook treatment control group, then a sample of 40 per group would be sufficient to reliably show a reduction of 10 days or more in the workbook group. Consistent with Hodgins and colleagues (28), clinical significance in the present study was defined as a reduction in cannabis by at least 50% or sustained abstinence for the preceding 30-days.

Trial interventions

Workbook

These participants received a mailed self-directed workbook. The workbook was developed based on the results of research that identified the most common behavioral and cognitive-motivational strategies used by individuals who have successfully recovered from CUD (25) **Table 1**]. It includes four core modules (self-assessment, goal setting, meeting your goal, and maintaining your goal). Examples of strategies are understanding the main reasons for using cannabis and reasons for changing (motivational), identifying and managing triggers (cognitive/behavioral), identifying and challenging patterns of thinking that increase risk of use (cognitive), and increasing social supports (behavioral). The workbook also provides information about provincial and territorial resources for further support if the self-directed approach is ineffective.

TABLE 1 Contents of the workbook and corresponding strategies.

No.	Content	Identified strategies from Stea et al. (25)
S0	**Introduction**	
	Information about cannabis use disorder, its signs, and cannabis withdrawal	
S1	**Self-assessment**	
	Is there a problem?	
	Understanding your cannabis use	
	Understanding your reasons for using cannabis	
S2	**Making your decision**	
	Understanding reasons for changing your cannabis use	Identifying reasons for resolution
	Pros and cons of cannabis use	Thinking about the negative consequences and the benefits of not using cannabis
	Choosing a change goal	
	Personal commitment to self	Accountability as a maintenance factor
S3	**Reaching your goal**	
	Triggers and cravings	
	Dealing with urges/cravings	Hobbies/distracting activities
	Identifying triggers	Identifying triggers
	Managing triggers	Stimulus control/avoidance
	Planning ahead	Identifying high risk situations
	Changing thinking	
	Identifying self-talk	
	Challenging unhelpful thoughts	Changing patterns of thinking and attitudes
	Increasing social supports	Decreasing time spend with users/increased time spent with non-users and social/family support
	Diet and exercise	Exercise/diet changes
	Focusing on goals and values	Setting and focusing on life goals
S4	**Maintaining your goal**	
	Planning ahead	Coping with stress and triggers
	Peer pressure and refusal skills	Exposure to peer pressure as a reason for relapse
	Slips and relapses	
	Dealing with other life Problems	

Workbook plus motivational interview

Participants assigned to the WMI condition received the self-directed workbook following a brief motivational interview conducted over Microsoft Teams with audio only. The motivational therapist contacted the participant as soon as possible to schedule the motivational interview, which were generally conducted within two weeks of the baseline assessment (M = 12.82; SD = 6.53).

The motivational telephone interaction was modified from the well-validated manualized MI protocol for gambling disorder. The interview attempted to explore ambivalence and strengthen the participants motivation for changing their cannabis use. The interview began with inviting participants to share their reasons for signing up for the study and

reasons for wanting to change their behavior. The motivational interviewing approach is guided by five therapeutic principles (47): acceptance of the individual and recognition that ambivalence is a normal process; development of discrepancies between the individual's current behavior and their goals or values; avoidance of argumentation; rolling with resistance; and supporting the individual's self-efficacy. The interviews ended with a brief description of the workbook and interviewers drew a connection between a specific workbook section and the client's own ideas for change. The interviews were an average 44.95 min in length (SD = 11.15; range 26-82) and were audiotaped.

Therapist adherence

MI interviewers (N = 6) were graduate students in a Clinical Psychology program who were trained in the MI protocol by a Clinical Psychologist who is experienced with training clinicians in MI. Training involved directed readings in MI, a training workshop, supervised role-plays, and supervision on two initial interviews. Interviewers were required to demonstrate competence in the MI protocol through role-plays. In the two initial interviews, interviewers were assessed in their ability to use 17 required elements in the MI protocol (e.g., addressing physical and emotional concerns; promoting self-efficacy; asking about previous change attempts) and three prohibited elements (providing unsolicited advice, using the "righting reflex," and confrontation). The range of required elements present in the interviews was 15 to 17 (M = 16.40). There were no instances of prohibited elements in the interviews reviewed.

Delayed workbook treatment control

These participants were assigned to a 3-month delayed treatment control condition. Participants were informed that they would receive the workbook following a waiting period of 3 months. Following the waiting period, participants invited to complete a follow-up assessment and to provide their address where the workbook could be mailed.

Baseline assessment

Measures

Demographic questionnaire

A lab-developed questionnaire recorded age, gender identity, ethnicity, marital status, level of education, and household income.

Cannabis use disorders identification test-revised [CUDIT-R]

The CUDIT-R (46) is an eight-item screening measure for problem cannabis use in the past 6-months. Scores of 8 or more indicate risky cannabis use, while scores of 12 or more suggest a possible CUD. It shows good internal reliability and concurrent validity (48), and high sensitivity and specificity for identifying moderate CUD with a threshold of 13 (49). The CUDIT-R was administered in the screening and baseline surveys to stratify the random assignment by CUDIT-R score, as reported in *Recruitment Procedures*. The internal reliability for the present study was α = 0.61.

Marijuana problem scale [MPS]

The MPS (13, 14) is a 19-item measure which assesses the impact of use in social, financial, work, physical health, cognition, self-esteem, motivation, and legal domains in the previous month. The number of problems on the MPS is sensitive to change, and can be used to assess changes in use-related problems after treatment (14). Internal reliability for the present study was α = 0.87.

Marijuana problem scale lifetime version [MPS-L]

The MPS-L (50) is a 16-item measure of lifetime problems associated with cannabis use. It yields a total score and two sub scores that reflect internal and external consequences. It is adapted from the MPS and shows good internal and test-retest reliability (50). Internal reliability for the present study was α = 0.87.

Cannabis engagement assessment [CEA]

The CEA (51) contains 30 questions that assess the quantity, frequency of use, and method of consumption for dried cannabis products (excluding edibles), cannabis concentrates, and edible products. For each method, several indices of cannabis engagement can be calculated, that integrate both frequency and quantity of use (e.g., the overall amount of cannabis product consumed through a given mode). It includes a question that assesses overall frequency of cannabis use in the previous 30-days. The overall quantity of cannabis use estimated across all three modes of cannabis in a single composite variable can also be calculated. Two additional sections assess other factors associated with cannabis use and history of use.

Screener for substance and behavioral addictions [SSBA]

The SSBA (52) is a brief screening instrument for self-attributed problems with four substances (alcohol, tobacco, cannabis, and cocaine) and six behaviors (gambling, videogaming, binge eating, shopping, sex, and work) in community samples. Scores range from 0 to 16, with higher scores indicating greater risk of addiction. It was developed from a larger pool of items that were generated by content-coding responses to open-ended questions asking individuals what signs or symptoms they felt were important indicators of problematic engagement (53). Internal consistency for the present study ranged from α = 0.77 (Cannabis) to α = 0.96 (Tobacco).

Kessler psychological distress scale [K10]

The K10 (54) is a brief, well validated measure of psychological distress that is sensitive to changes over time (54, 55). The internal reliability for the present study was $\alpha = 0.93$.

World health organization quality of life-8 item scale [WHOQoL-8]

The WHoQoL-8 (56) is an eight-item version of the longer WHOQoL, a self-report measure of quality of life. It has robust psychometric properties, and correlates strongly with the WHOQoL (56). Scores range from 1 ("Very Satisfied") to 5 ("Very Dissatisfied"). An average score across items is calculated, where higher values indicate lower quality of life. Internal consistency for the present study was $\alpha = 0.84$.

Follow-up assessment

Follow-up assessments were conducted at 3-months and 6-months post-baseline with a completion rate of 82.80 and 76.34%, respectively. Follow-up rates did not differ significantly by group, $ps \geq 0.94$.

At each follow-up assessment, the following measures were re-administered: CEA, MPS, K10, WHOQoL-8, and change goal. Participants also were asked whether they had utilized other forms of treatment in the previous 3-months, how successful they had been at reaching their treatment goal (on a scale of 0-"nothing has changed" to 10-"I reached my goal"), how helpful they found the workbook at helping them work toward their goal (on a scale of 0 – "I could have made as much progress without the workbook" to 10-"the workbook has been very helpful"), and how often they utilized the workbook (0 – "Never" to 5 – "Daily").

Data analysis

Analyses were conducted using SPSS version 28.0 except generalized equation modeling (GEE), which was done in R (42) using *geepack* (57). Two primary outcome variables were decided *a priori* to assess the success of the intervention at producing a statistically significant improvement: mean number of days of cannabis use and the overall amount of cannabis used in the previous month. Self-rated improvement, psychological distress, and quality of life were used as secondary outcome variables. A missing values analysis that also included baseline characteristics showed that data were missing completely at random, Little's MCAR test $\chi^2 = 3599.86$, $p = 0.22$). Thus, analyses were conducted on the intent-to-treat sample with all available data.

For the 3- and 6-month outcomes, the cannabis use variables were calculated for the 30 days prior to pretreatment and prior to each follow-up assessment. Extreme outliers, identified using the 3*interquartile range method, were recoded as 1 less/greater than the smallest/largest non-extreme value (58). Three data points were identified as extremely low at baseline and recoded. Given different units of measurement across modes of cannabis, the total amount of cannabis product used for each mode was first standardized using a z-score transformation. Z-scores were calculated separately for each group and time point. An average standardized score was calculated to reflect the overall amount of cannabis used across modes. Extreme outliers were recoded using the same method as for days of cannabis use. For quantity, 42 data points were identified as extremely high outliers and recoded.

For the three-month control group comparison of frequency of cannabis use, a one-way analysis of covariance (ANCOVA; three groups) was conducted contrasting the WB and WMI groups with the DT group, covarying the pretreatment value. The variable reflecting the overall quantity of cannabis use was highly skewed. Therefore, we ran a quade non-parametric ANCOVA (59); 3 groups], covarying the pretreatment value. Quade's ANCOVA tests the equality of the residuals among groups using ranked covariates and the response variable (60). Additionally, to examine clinical significance, we compared a categorization between groups of the percentage of participants abstinent, improved (50% or greater reduction in days of cannabis use), and not improved (Hodgins et al. (28) using a monte carlo chi-square simulation with 10,000 replications given several low cell sizes.

To conduct the hypothesized comparisons of groups over the 6-month follow-up period, generalized equation estimations (GEE) were used for separate days of cannabis use and quantity of cannabis used, with participants as the subject variable, group as a fixed factor, time (0, 3, 6) as a fixed covariate, and assuming an AR1 correlation structure. Those who had a baseline assessment without completing follow-up assessments contributed only baseline data to the GEE model estimates. The slopes representing improvement from baseline to three months were expected to be larger than the slope from 3 to 6 months. Therefore, we modeled these slopes using a piece-wise linear approach. The DT group was coded as the reference condition.

GEE analyses also compared groups at 3-months and 6-months follow-up on secondary outcome variables: cannabis-related problems, psychological distress, and quality of life. Self-rated improvement across groups was compared using one-way ANOVA.

Results

Participation flow

Figure 1 provides the Consolidated Standards of Reporting Trials (CONSORT) style flow-chart of participants. Between December 2020 and April 2021, a total of 774 people were

recruited, of whom 405 (52.33%) met initial eligibility criteria. Of the eligible participants, 255 (62.96%) completed the baseline survey. A further 69 participants were excluded from the study. See Figure 1 for a list of reasons for exclusion. "Other" reasons were idiosyncratic and impacted the ability to contact participants, such as emails not able to be delivered or a US mailing address. The remaining participants (n = 186; 72.94%) were randomly assigned to one of three groups, stratified by gender and problem severity. Of the 186 participants enrolled and randomly assigned to a condition, three discontinued and withdrew their data.

Baseline characteristics

The final sample consisted of 183 participants (86 male; 46.99%; Table 2), aged 18 to 60 (M = 30.85; SD = 9.67), mostly Caucasian (n = 151; 82.51%), single (n = 112; 61.20%), and employed (n = 144; 78.69%).

Cannabis engagement characteristics at baseline are reported in Table 3. Participants reported using cannabis an average of 26.09 days in the past month (SD = 6.46). A majority of participants had a history of at least one previous attempt to reduce their cannabis use (n = 161; 87.98%), but few had ever sought treatment (n = 31; 16.94%). Most participants were interested in reducing their use versus stopping completely (n = 37; 20.22%).

Regarding engagement in other potentially addictive substances and behaviors, participants showed the highest scores on the SSBA subscales of cannabis (M = 9.66, SD = 3.90) tobacco (M = 7.15, SD = 5.06), and eating (M = 5.87, SD = 4.07). The average SSBA subscale scores across each group and the entire sample are shown Supplementary Table 1.

Among participants who were randomly assigned to the condition which included a motivational telephone interaction, those who completed and did not complete the interview were compared on the variables displayed in Tables 2, 3, and Supplementary Table 1. No significant differences emerged on any demographic characteristics or SSBA subscale scores, ps > 0.06. Not assuming equal variances, individuals who did not complete the MI interview reported greater THC in the concentrated cannabis products used compared to individuals who completed the interview, $t(31.49) = -2.41$, $p = 0.02$, and a higher frequency of cannabis use across modes, $t(55.90) = 2.30$, $p = 0.03$, than individuals who completed the interview.

Participants who did and did not complete the follow-up assessments at 3 and 6 months were also compared on the same variables. Individuals with fewer daily reported sessions of dry cannabis use were less likely to complete the 3-month follow-up, $t(176) = -1.98$, $p = 0.049$. Individuals with higher scores on the MPS-L were also less likely to have completed the follow-up at three months, $t(178) = 2.40$, $p = 0.01$, and at 6 months, $t(178) = 1.81$, $p = 0.04$. Not assuming equal variances, individuals who did not complete the 6-month follow-up also reported significantly greater THC in their concentrated cannabis products, $t(60.41) = 2.93$, $p = 0.002$, but less THC in edibles, $t(75.88) = -2.44$, $p = 0.01$.

Finally, participants were asked whether they had sought other professional treatment during the follow-up window. The overall proportion of participants seeking other professional support was 18.46% at 3-months and 22.46% at 6-months, with no between-group differences, ps = 0.84 and.43. ANCOVA revealed that seeking other professional support did not predict the frequency of cannabis use at 3-months, $F(1, 144) = 3.12$, $p = 0.08$, or at 6-months, $F(1, 130) = 0.08$, $p = 0.77$. Neither did it predict the proportion of cases improved or abstinent at 3-months, $\chi^2(2) = 5.84$, $p = 0.08$, or 6-months, $p = 0.81$.

Group comparisons at 3-months

Results partially supported our first hypothesis that participants in the WMI and WB groups would show lower frequency of cannabis use at 3-months compared to the DT group. For days of cannabis use, an ANCOVA was conducted, covarying the days of cannabis use in the month prior to beginning the study[1]. Although the assumption of homogeneity of variances was not met, Levene's $F(2, 148) = 3.73$, $p = 0.03$, the F-test is robust to the variance ratio and coefficient of sample size variation observed (61). Therefore, it was appropriate to move forward with the untransformed data. There was a statistically significant difference in days of cannabis use between the groups, $F(1, 2) = 5.16$, $p = 0.007$, partial $\eta^2 = 0.07$. Controlling for baseline days of cannabis use, frequency of use at three months was significantly lower WMI group (M = 16.83, SD = 11.97) versus the DT group (M = 22.67, SD = 9.55), mean difference of −3.83, 95% CI [−7.27, −0.38], $p = 0.03$. However, days of cannabis use did not differ significantly between the WB (M = 22.76, SD = 8.99) and DT group, mean difference = 1.75, 95% CI [−1.64, 5.15], $p = 0.31$. Results also supported our third hypothesis that participants in the WMI group would show a greater reduction than participants in the WB group, mean difference = −5.58, 95% CI [−9.08; −2.08].

The proportion of participants abstinent, improved (50% or greater reduction in days of cannabis use), and not improved are shown in Table 4. Monte carlo simulation analyses showed a statistically significant association between group and outcomes $\chi^2(4) = 9.52$, $p = 0.046$; a greater number of individuals in the WMI group improved or achieved abstinence compared to the other two groups at $p < 0.05$.

Participants quantities of cannabis used were compared with Quade's ANCOVA, covarying the baseline quantity. There was a statistically significant difference in quantity of cannabis

1 The analysis was rerun without recoding the extreme outliers and yielded similar results.

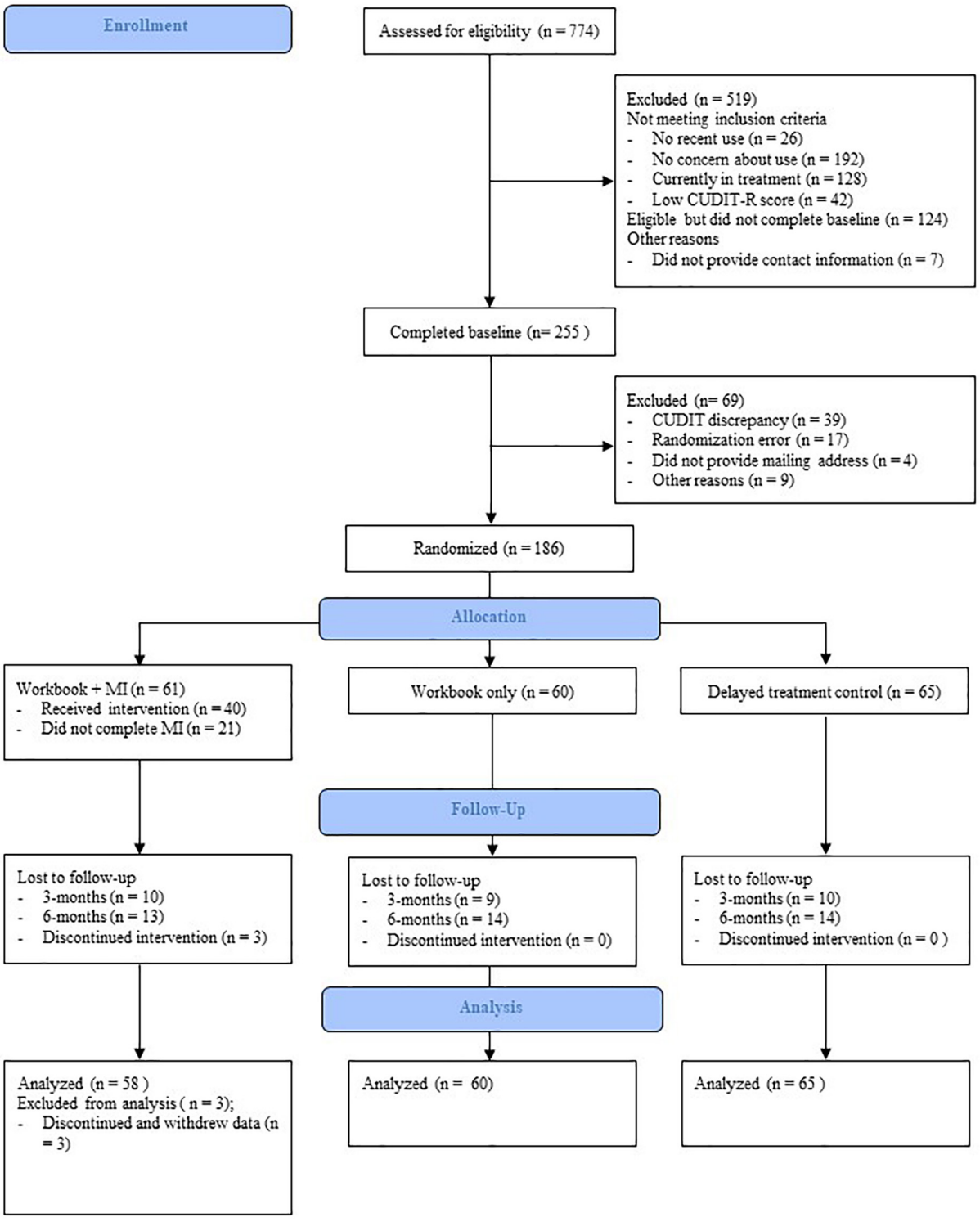

FIGURE 1
Consolidated Standards of Reporting Trials (CONSORT) style flow-chart of participant recruitment and retention.

used between groups, Quade's $F(2, 147) = 3.12$, $p = 0.047$. Consistent with hypothesis 3, quantity of cannabis use was significantly lower in the WMI group compared to the WB group, $t(147) = -2.37$, $p = 0.02$). When the analysis was rerun without recoding the extreme outliers, the significant effect was no longer present.

TABLE 2 Participant demographic characteristics by group and across entire sample.

Characteristic, *n* (%)	Workbook + MI (*n* = 58)	Workbook only (*n* = 60)	Delayed workbook treatment (*n* = 65)	Total (*N* = 183)
Age, *M* (SD) *years*	30.48 (9.26)	31.32 (10.70)	30.74 (9.15)	30.85 (9.67)
Gender				
Female	28 (48.28)	28 (46.67)	30 (46.15)	86 (46.99)
Male	27 (46.55)	29 (48.33)	30 (46.15)	86 (46.99)
Non-binary	2 (3.45)	3 (5.00)	3 (4.62)	8 (4.37)
Other	1 (1.72)	–	2 (3.08)	3 (1.64)
Marital status				
Single (not legally married)	35 (60.34)	40 (66.67)	37 (56.92)	112 (61.20)
Legally married	6 (10.34)	7 (11.67)	7 (10.77)	20 (10.93)
Common-law	12 (20.69)	11 (18.33)	18 (27.69)	41 (22.40)
Separated	3 (5.17)	1 (1.67)	–	4 (2.19)
Divorced	2 (3.45)	1 (1.67)	3 (4.62)	6 (3.28)
Education				
High school or less	21 (36.31)	28 (46.67)	17 (26.15)	66 (36.07)
Trades or apprenticeship	1 (1.72)	3 (5.00)	–	4 (2.19)
College certificate/diploma	11 (19.97)	9 (15.00)	15 (23.08)	35 (19.13)
Some university	5 (8.62)	5 (8.33)	6 (9.23)	16 (8.74)
Undergraduate degree	12 (20.69)	9 (15.00)	16 (24.52)	37 (20.22)
Graduate degree	8 (13.79)	6 (10.00)	11 (16.92)	25 (13.66)
Employment[a]				
Full-time	22 (37.93)	28 (46.67)	30 (46.15)	103 (56.28)
Part-time	16 (27.59)	10 (16.67)	15 (23.08)	41 (22.40)
Unemployed	8 (13.79)	15 (25.00)	12 (18.46)	29 (15.85)
Retired	1 (1.72)	1 (1.67)	–	2 (1.09)
Student	15 (25.86)	13 (21.67)	17 (26.15)	45 (24.59)
Other	6 (10.34)	3 (5.00)	3 (4.62)	12 (6.56)
Income				
Under $10,000	6 (10.34)	6 (10.00)	3 (4.62)	15 (8.20)
$10,000 to $39,999	22 (37.93)	22 (36.67)	26 (40.00)	70 (38.35)
$40,000 to $69,999	13 (22.41)	13 (21.67)	16 (24.62)	42 (22.95)
$70,000 to $99,999	10 (17.24)	10 (16.67)	9 (13.85)	29 (15.85)
Over $100,000	7 (12.07)	9 (15.00)	11 (16.92)	27 (14.75)
Ethnicity[a]				
Caucasian	47 (81.03)	46 (76.67)	58 (89.23)	151 (82.51)
South Asian	2 (3.45)	3 (5.00)	4 (6.15)	9 (4.92)
Black	1 (1.72)	1 (1.67)	2 (3.08)	4 (2.19)
Latin American	3 (5.17)	2 (3.33)	–	5 (2.73)
Indigenous	2 (3.45)	5 (8.33)	2 (3.08)	9 (4.92)
Other	6 (10.34)	4 (6.67)	1 (1.54)	11 (6.01)

[a]participants could endorse multiple options.

Group comparisons over six months[2]

The groups means at baseline and the two follow-up periods are displayed in Table 5. For days of cannabis use, GEE modeling revealed that the baseline to 3-month slopes differed significantly from zero, *ps* < 0.001. Results also partially supported our second hypothesis; the baseline to 3-month slope for the WMI group differed significantly from the DT group (see Table 6 and Figure 2). However, the slope for the WB group did not differ significantly from the DT condition. Consistent with hypothesis 2, when the WMI group was contrasted against the WB group, a significant effect emerged. Between baseline and 3-months, individuals in the WMI condition showed a significantly greater reduction in days of cannabis use than individuals in the WB alone group, *Est(SE)* = −5.23(1.84), Wald = 8.09, $p = 0.005$. The 0- to 6-month slope was significant, *Est(SE)* = −5.99(1.17), Wald = 26.39, $p < 0.001$. However, the 3-to 6-month slope only approached significance, $p = 0.06$. The 3- to 6-month slope for the WMI

2 GEE models were rerun without recoding the extreme outliers and yielded similar results.

TABLE 3 Cannabis engagement characteristics and scores on external measures at baseline across entire sample.

Characteristic, *M (SD)*	Workbook + MI (*n* = 58)	Workbook only (*n* = 60)	Delayed workbook treatment (*n* = 65)	Total (*N* = 183)
Use - Dried Cannabis Product, *n (%)*	56 (96.55)	59 (98.33)	64 (98.46)	179 (97.81)
Frequency (days)	24.13 (8.89)	24.08 (8.56)	23.48 (8.62)	23.88 (8.64)
Daily sessions	3.12 (1.63)	3.09 (1.98)	2.94 (1.75)	3.04 (1.79)
Daily product (grams)	3.70 (8.47)	2.11 (2.16)	2.51 (4.22)	2.75 (5.52)
Average THC (%)	20.63 (8.62)	19.57 (3.38)	20.42 (5.68)	20.20 (6.18)
Use-Concentrated cannabis products, *n (%)*	36 (62.07)	27 (45.00)	33 (50.77)	96 (52.46)
Frequency (days)	13.75 (11.36)	9.56 (9.98)	9.85 (9.55)	11.23 (10.46)
Daily sessions	2.83 (2.50)	4.67 (9.32)	2.48 (1.91)	3.32 (5.30)
Daily product (hits)	24.67 (43.68)	23.73 (48.08)	14.81 (19.30)	21.05 (38.52)
Average THC (%)	58.33 (26.66)	59.04 (22.62)	63.47 (20.21)	60.28 (23.33)
Use-Edible products, *n (%)*	30 (51.72)	36 (60.00)	45 (69.23)	111 (60.66)
Frequency (days)	7.60 (8.87)	5.39 (5.61)	5.56 (5.07)	6.05 (6.47)
Daily sessions	2.13 (1.74)	1.50 (0.94)	1.53 (0.99)	1.68 (1.24)
Daily product (grams)	19.32 (43.21)	7.21 (10.70)	12.22 (17.45)	12.27 (24.09)
Average THC per session (mg)	155.34 (237.72)	77.37 (113.47)	104.97 (204.96)	110.59 (192.61)
Frequency of overall cannabis use (days)	25.38 (7.17)	26.11 (6.59)	26.72 (5.65)	26.09 (6.46)
Age of first use	15.71 (2.58)	16.24 (3.67)	16.51 (3.71)	16.16 (3.38)
Age of regular use	19.79 (4.85)	20.93 (8.66)	20.43 (7.26)	20.39 (7.10)
Years of regular use	10.26 (9.08)	9.31 (9.58)	9.38 (9.93)	9.64 (9.51)
History of reduce attempts, *n (%)*	50 (86.21)	56 (93.33)	55 (84.62)	161 (87.98)
History of treatment seeking, *n (%)*	16 (27.59)	6 (10.00)	9 (13.85)	31 (16.94)
Abstinence goal, *n (%)*	11 (18.97)	12 (20.00)	14 (21.54)	37 (20.22)
CUDIT-R	22.24 (4.29)	22.53 (4.52)	22.26 (4.45)	22.34 (4.40)
MPS	12.83 (6.86)	12.88 (7.28)	11.95 (6.21)	12.54 (6.76)
MPS-L	13.84 (6.77)	12.47 (6.46)	12.94 (6.80)	13.07 (6.66)
K10	29.81 (7.98)	27.48 (8.72)	27.80 (8.75)	28.33 (8.52)
WHOQoL-8	3.08 (0.72)	3.14 (0.84)	2.94 (0.77)	3.05 (0.78)

CUDIT-R, cannabis use disorders identification test-revised; MPS, marijuana problem scale; MPS-L, marijuana problem scale-lifetime version; K10, kessler psychological distress scale; WHOQoL-8, world health organization quality of life-8 item scale.

group continued to differ significantly from the DT group, but in the opposite predicted direction, *Est(SE)* = 4.62(2.11), Wald = 4.78, $p = 0.03$. At 6 months, the means for the DT group did not differ significantly from the WB group, $p = 0.90$.

For quantity of cannabis use, a significant effect of time emerged, $\chi^2(2) = 12.20$, $p = 0.002$ (Table 6 and Figure 3). However, no between-group effects were significant from baseline to 3-months, or from 3- to 6-months, $ps \geq 0.06$.

TABLE 4 Classification of outcome based on days of cannabis use *n* (%).

Follow-up	Workbook + MI	Workbook only	Waitlist control
3 months	*n* = 47	*n* = 47	*n* = 55
Abstinent	5 (10.64)	1 (2.13)	1 (1.82)
Improved	12 (25.53)	6 (12.77)	8 (14.55)
Not improved	30 (62.83)	40 (85.11)	46 (83.64)
6 months	*n* = 45	*n* = 43	*n* = 48
Abstinent	4 (8.89)	3 (6.98)	1 (2.08)
Improved	11 (24.44)	10 (23.26)	8 (16.67)
Not improved	29 (64.44)	30 (69.77)	39 (81.25)

Secondary outcomes

GEE modeling compared groups on problems associated with cannabis use (MPS), psychological distress (K10) and quality of life (WHOQoL-8). Across outcomes, a significant effect of time emerged, $ps < 0.001$. However, the groups did not differ significantly across time from one another, $ps > 0.13$.

Participants were asked at each follow-up how successful they felt they had been at reaching their treatment goal in the preceding 3-months. A one-way ANOVA compared

TABLE 5 Means (and SDs) for primary and secondary outcomes at baseline and follow-up assessments.

	Baseline	3 months	6 months
Days			
Workbook + MI	25.38 (7.17)	16.83 (11.97)	18.35 (11.73)
Workbook only	26.11 (6.59)	22.76 (8.99)	20.07 (10.93)
Delayed workbook treatment	26.72 (5.65)	22.67 (9.55)	20.67 (9.37)
Amount[a]			
Workbook + MI	0.08 (0.67)	−0.12 (0.10)	−0.08 (0.20)
Workbook only	0.04 (0.94)	−0.08 (0.16)	−0.08 (0.19)
Delayed workbook treatment	−0.12 (0.18)	−0.11 (0.08)	−0.08 (0.18)
MPS			
Workbook + MI	12.83 (6.86)	8.72 (7.77)	8.91 (7.52)
Workbook only	12.88 (7.28)	10.23 (6.40)	9.73 (8.19)
Delayed workbook treatment	11.95 (6.21)	9.41 (6.57)	8.50 (5.69)
K10			
Workbook + MI	29.81 (7.98)	25.43 (8.17)	25.56 (8.10)
Workbook only	27.48 (8.72)	24.60 (8.33)	23.98 (7.34)
Delayed workbook treatment	27.80 (8.75)	25.13 (8.68)	25.02 (8.42)
WHO QoL			
Workbook + MI	3.08 (0.72)	2.45 (0.68)	2.70 (0.75)
Workbook only	3.14 (0.84)	2.38 (0.86)	2.64 (0.81)
Delayed workbook treatment	2.94 (0.77)	3.19 (0.77)	2.81 (0.84)
Self-Rated Improvement			
Workbook + MI	–	5.24 (3.02)	4.51 (2.86)
Workbook only	–	4.00 (2.00)	4.33 (2.80)
Delayed workbook treatment	–	3.30 (2.71)	4.18 (2.32)

[a]Z-score transformed variable. MPS, marijuana problem scale; K10, kessler psychological distress scale; WHOQoL-8, world health organization quality of life-8 item scale.

participants self-rated success at each follow-up. Self-rated success differed significantly between groups at 3-months, $F(2, 145) = 6.02$, $p = 0.003$, but not at 6-months, $p = 0.90$. *Post hoc* analyses with the holm-bonferroni adjustment indicated that the participants in the WMI group had significantly higher self-rated success ($M = 5.24$, SD = 3.02) at 3-months than both the DT ($M = 3.43$, SD = 2.83) and WB ($M = 4.00$, SD = 1.98) groups, ps.048 and <0.001. The difference between the WB and DT groups was not significant, $p = 0.82$. No significant between-group differences emerged on the perceived helpfulness of the workbook or how often the workbook was used at either 3-months or 6-months, ps $\geq$ 0.14. A follow-up linear regression analysis examined whether the frequency of workbook use predicted cannabis use at 3- and 6-months follow up. Controlling for the frequency of cannabis use at baseline, workbook use did not predict cannabis use at 3-months follow-up, $p = 0.09$. However, frequency of the workbook between 3- and 6-months predicted days of cannabis use at 6-months follow-up, $B = -3.16$, SE = 1.03, $t = -3.06$, $p = 0.003$.

Discussion

Overall, the primary hypotheses were partially supported. The workbook in combination with a motivational interview (WMI) demonstrated its utility at reducing the frequency of cannabis use compared to both the workbook (WB) and delayed workbook treatment (DT) condition. Individuals in the WMI condition reported significantly fewer days of cannabis use at 3-months follow-up compared to those who received the workbook alone (WB) or in the delayed workbook treatment group (DT), lending support for hypotheses 1 and 3. When considering the number of participants who had improved or achieved abstinence across the first three-months, a similar pattern emerged; Individuals in the WMI group showed significantly greater rates of abstinence compared to the other groups than would be expected by chance.

Between baseline and 3-months, individuals in the WMI condition showed a significantly greater reduction in days of cannabis use than individuals in the WB alone group. The 3-to 6-month slope for the DT group only approached significance, indicating that continued improvement slowed after 3-months. This is not surprising, given the level of improvement observed in this group before receipt of the workbook. Surprisingly, the 3- to 6-month slope for the WMI group continued to differ significantly from the DT group, but in the opposite predicted direction, indicating that use rose slightly between 3- and 6-months. Future research might consider whether a booster MI session would help sustain the changes made in the first three months. Walker and colleagues (62) previously found that MI maintenance check-ups at 1- and 4-months post-treatment led to greater rates of abstinence than participants who did not receive subsequent MI sessions following a CBT/MET treatment for CUD. It is possible that additional MI as needed could help sustain the greater rate of change that was seen in the WMI group between 0- and 3-months.

For quantity of cannabis use, a significant effect of time emerged, but no between-group effects were significant from baseline to 3-months, or from 3- to 6-months. This was somewhat surprising, given the changes in the frequency of cannabis use that was observed in the current study. One possible explanation for the effect is that individuals may have initially increased the quantity of their cannabis use while attempting to reduce the overall frequency. Indeed, **Figure 3** shows a small increase in overall quantity of use between baseline and 3 months, before a decrease between 3- and 6-months. However, we cannot conclude whether or not this effect was simply due to chance, as none of the results were statistically significant. We were also required to z-score transform the measures of quantity, which would have reduced variability and possibly reduced the power to statistically detect changes in quantity of cannabis.

All groups showed similar rates of improvement in self-reported quality of life, reduced psychological distress, and fewer problems associated with their cannabis use through the course of the study. It is unclear whether this is due to the changes in the frequency and quantity of cannabis use that was observed across groups as well. Similarly, no

TABLE 6 Parameter estimates for days and quantity of cannabis use from GEE modeling.

Effect	Parameter estimate	SE	Wald	*P*	95% CI
Days of cannabis use					
DT Intercept	26.43	0.75	1253.87	< 0.001	24.96, 27.90
WMI	−1.10	1.19	0.86	0.35	−3.45, 1.24
WB	−0.69	1.69	0.34	0.56	−2.98, 1.62
Baseline to 3-month slope					
DT	−3.94	1.11	12.53	< 0.001	−6.14, −1.75
WMI	−4.21	1.82	5.34	0.02	−7.79, −0.63
WB	1.02	1.59	0.41	0.52	−2.12, 4.15
3-month to 6-month slope					
DT	−2.42	1.32	2.37	0.07	−5.02, 0.18
WMI	4.62	2.11	4.78	0.03	0.46, 8.79
WB	−0.23	1.78	0.02	0.90	−3.73, 3.28
Quantity of cannabis use (Composite)					
DT Intercept	−0.07	0.06	1.34	0.25	−0.18, 0.05
WMI	−0.09	0.06	1.96	0.16	−0.21, 0.04
WB	−0.11	0.06	3.42	0.06	−0.22, 0.01
Baseline to 3-month slope					
DT	0.06	0.09	0.42	0.52	−0.11, 0.23
WMI	0.02	0.11	0.05	0.83	−0.20, 0.24
WB	0.14	0.13	1.10	0.30	−0.12, 0.389
3-month to 6-month slope					
DT	−0.12	0.07	2.62	0.06	−0.25, 0.005
WMI	0.04	0.09	0.18	0.68	−0.15, 0.23
WB	−0.09	0.11	0.69	0.41	−0.30, 0.12

The delayed workbook treatment (DT) group is the reference condition to which the workbook plus MI (WMI) and the workbook only (WB) groups are compared CI, confidence interval.

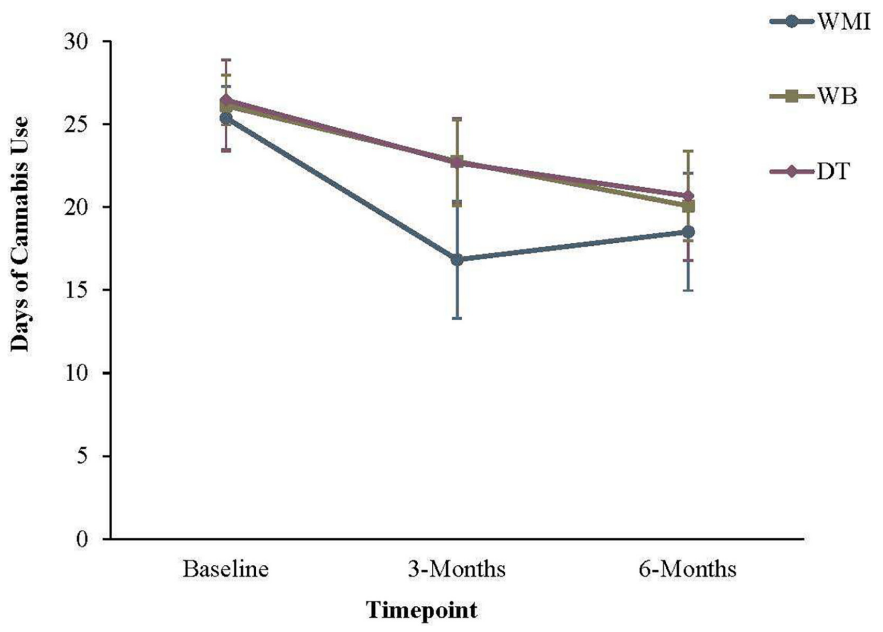

FIGURE 2
Frequency of cannabis use in the previous 30 days. Error bars represent the 95% confidence interval for that group at a given timepoint. WMI, workbook plus motivational interview group; WB = workbook only group; DT = delayed workbook treatment group.

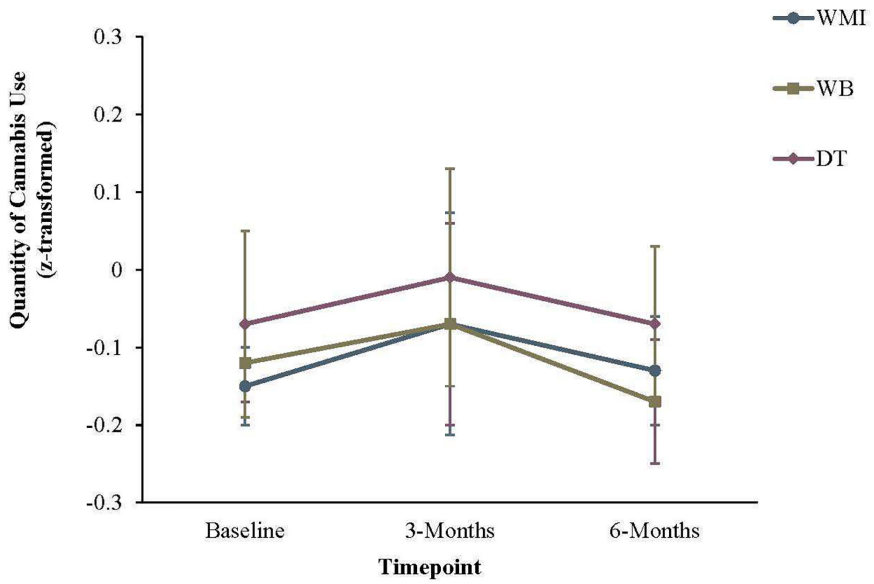

FIGURE 3
Quantity of cannabis use in the previous 30 days. Error bars represent the 95% confidence interval for that group at a given timepoint. WMI, workbook plus motivational interview group; WB, workbook only group; DT, delayed workbook treatment group.

significant between-group differences emerged on the perceived helpfulness of the workbook or how often the workbook was used at either 3-months or 6-months. However, linear regression analyses revealed that while frequency of workbook use in the first three months did not predict frequency of days of cannabis use at the 3 month-follow-up, use between 3- and 6-months predicted days of cannabis use at the 6-month follow-up. This suggests that while continued improvement slowed after the first 3-months, higher use of the workbook predicted lower rates of cannabis use at 6-months follow-up. This finding lends some support to the clinical utility of the workbook itself.

To our knowledge, this is the first study to examine the utility of a self-directed treatment workbook for problematic cannabis use as opposed to web-based treatment programs (32, 33). In contrast to the study by Rooke et al. (32) and our own hypotheses, we found no difference between the workbook alone and the control group on frequency of cannabis use at 3-months follow-up. In our study, the frequency of cannabis use decreased across participants, including those in the DT condition. However, previous research has also shown that problematic cannabis use can change over time, without formal intervention (25). Participants in the current study were motivated to reduce their cannabis use and many had attempted to change their cannabis in the past. Additionally, some participants, including those in the DT condition, sought other supports through the duration of this study, demonstrating a continuing desire to change their cannabis use. It is also possible that completion of the baseline assessment heightened participants' awareness of their current problems and thus increased their motivation to change. The baseline assessment included questions designed to assess problems associated with cannabis use, severity, and frequency. These areas are also explored in brief interventions, which aim to increase awareness and motivation for change (63, 64). Similar strategies and tools are also included in the workbook to support self-assessment and reflection. Thus, the need to include a detailed baseline assessment may have confounded the benefit of the workbook.

Several limitations of this study should be noted. First, because the delayed treatment period was limited to 3-months, it is not possible to examine the efficacy of the intervention for longer follow-up to a no-intervention group. As noted, all participants reduced their cannabis use in the first three months, at which point DT participants then received the workbook. It is possible that access to the workbook contributed to the continued changes between 3- and 6-months, whereas without access, rate of change would have slowed to a greater extent. As noted, using the workbook more frequently predicted lower rates of cannabis use at 6-months follow up. A second limitation is that quantity of cannabis use was measured by averaging z-score transformed measures of quantity across the three modes of cannabis use. This inherently creates challenges with interpretability and possibly limited our ability to detect between-group differences. Unfortunately, the field lacks a standardized method of assessing quantity of cannabis consumption across various modes. As previously described (51), participants struggle to estimate the amount of concentrated cannabis products used and so the CEA asks participants to report the number of "hits" rather than milligrams of cannabis itself. The most commonly used concentrate product is oil for vaping (51), where CBD and THC

are suspended in an oil solution with varying density. This makes it impossible to calculate the amount of cannabis itself consumed in each hit. Thus, we can estimate the amount of product used, though not the amount of cannabis. Nevertheless, with the composite variable, we were able to track changes in cannabis consumption over time and across multiple modes of use. Other studies, such as Rooke and colleagues (32) did not assess cannabis use across the myriad ways in which it can be consumed. A third related limitation is that assessing the frequency of cannabis use is also an imperfect outcome variable, given that some people sought to achieve abstinence rather than reduce their cannabis use. Fourth, we were unable to explore the effects of the intervention on THC quantity, or the influence of THC quantity on the results. Participants inconsistently reported their THC usage, with a majority not able to provide an estimate. As such, THC quantity was an unreliable index of use. Fifth, we estimated the sample size needed to detect a reduction of 10 days or more of cannabis use, though the intervention did not lead to a reduction of that amount. Thus, the study may have been underpowered. However, the results from this study can inform the target sample size of future research. Sixth, participants self-reported their cannabis use and we did not include an objective measure or collateral reports. However, it was not feasible to collect more objective measures in the current study, as we recruited participants from across Canada. Additionally, the sample included participants who were interested in a low-intensity treatment. Collection of urinalysis or saliva would have changed the representativeness of the sample and may have greatly increased attrition rates. Previous research has found high rates of concordance between urinalysis or collateral information and rates of abstinence [e.g., (62)]. This strengthens confidence in the validity of the self-reported cannabis outcomes.

Conclusion and future directions

The current study highlighted the utility of a brief motivational interview in combination with a self-directed workbook at promoting changes in cannabis use. Given many individuals with problematic cannabis use do not seek formal treatment (21, 22), this self-directed intervention has the potential to fill an important need in that the self-directed intervention can attract individuals who wish to recover with minimal professional support.

Individuals who use cannabis are also diverse in terms of both demographic factors and treatment goals and needs. However, many treatment programs emphasize only abstinence as a recovery outcome (9), rather than also supporting moderated use. This may partly explain why treatment-assisted participants with moderation goals are less likely to recommend treatment-assisted recovery (39). As such, a range of intervention possibilities of varying intensities, and the ability to personalize treatment goals is ideal (5). A stepped-care approach may enhance the provision of treatment for CUD by providing individuals with the opportunity to choose a level of intervention and treatment that is consistent with their goals and preferences. The workbook package tested in this study is sensitive to individual treatment goals, whether abstinence or controlled use. In fact, most participants were interested in reducing their use rather than stopping completely.

We have identified several avenues of future research. First, it would be beneficial to consider the efficacy of the intervention in a larger sample and over a longer follow-up period. As noted, an additional booster MI phone call could help sustain the changes made in the first three months and consequently, this should be investigated. Second, while stepped-care models consider many elements of an integrated public health response to preventing and treating problematic cannabis use, little research has sought to integrate such elements. Future research may benefit from examining uptake of our self-directed intervention through other resources within a stepped-care framework. For example, we previously proposed that this intervention could be integrated with Screening, Self-Management and Referral to Treatment (SSMRT), a secondary prevention platform designed to reduce harms from cannabis use, provide information, and connect interested individuals to appropriate treatments (65). Third, future research would also benefit from increasing our understanding of individual differences in treatment responsiveness among individuals with various demographic and treatment goals, and who are interested in self-directed change. Such information could inform refinement of treatment resources that are sensitive to the experiences and needs of individuals with cannabis problems. Relatedly, CUD is commonly comorbid with other mental health concerns (66). Future research may also consider the influence of comorbid mental health conditions on responsiveness to self-directed treatment. This line of research would also shed further light on important considerations for a successful public health approach.

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 University of Calgary Conjoint Faculties Research Ethics Board (CFREB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS and DH contributed to the conceptualization and design of the study. JS and MK critically reviewed the design and grant proposal. MS performed the statistical analyses and drafted the first manuscript. DH wrote parts of the manuscript and edited subsequent versions. JS and MK reviewed the manuscript for critical content. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

This project was conducted as part of MS dissertation.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1015443/full#supplementary-material

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Selecting the appropriate hurdles and endpoints for pentilludin, a novel antiaddiction pharmacotherapeutic targeting the receptor type protein tyrosine phosphatase D

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Substance use disorders provide challenges for development of effective medications. Use of abused substances is likely initiated, sustained and "quit" by complex brain and pharmacological mechanisms that have both genetic and environmental determinants. Medical utilities of prescribed stimulants and opioids provide complex challenges for prevention: how can we minimize their contribution to substance use disorders while retaining medical benefits for pain, restless leg syndrome, attention deficit hyperactivity disorder, narcolepsy and other indications. Data required to support assessments of reduced abuse liability and resulting regulatory scheduling differs from information required to support licensing of novel prophylactic or therapeutic anti-addiction medications, adding further complexity and challenges. I describe some of these challenges in the context of our current efforts to develop pentilludin as a novel anti-addiction therapeutic for a target that is strongly supported by human and mouse genetic and pharmacologic studies, the receptor type protein tyrosine phosphatase D (PTPRD).

KEYWORDS

receptor type protein tyrosine phosphatase, lapse doses, relapse, antiaddiction drug development, inhibitors of protein tyrosine phosphatase

Introduction

Urgent public health needs

Development of safe and effective medications to aid prevention and treatment of stimulant, opioid and stimulant + opioid use disorders are urgent public health needs. I can describe some of the statistics using published materials and some *via* links to websites for material that is not published.

Stimulants

Almost 20 metric tons of amphetamines and almost 9 metric tons of lisdexamphetamine are prescribed *via* >30 million annual prescriptions in the US (1). Many were prescribed

chronically for indications including ADHD and narcolepsy.[1] 1.8% of the US population reported missuse of a prescribed stimulant.[2] 0.7% of the US population used an amphetamine from a licit or illicit source, almost 7.5 million Americans reported cocaine or methamphetamine use and almost 1.8 million reported a cocaine or amphetamine use disorder (see text footnote 2). Despite the lack of any FDA-approved medication for cocaine or methamphetamine use disorders, there are about 200,000 annual admissions to a stimulant use disorder treatment program (see text footnote 2).

Opioids

More than 142 million opioid prescriptions are written annually in the US,[3] many prescribed chronically for chronic pain. More than 10 million Americans misuse opioids/year (745,000 using heroin and 9.7M prescription pain relievers) and almost 50,000/year die from this use.[4]

Stimulants + opioids

There is increasing co use of opioids along with stimulants (though not necessarily from "speedball" preparations that are intentionally co-injected). Past-year methamphetamine use among people using heroin rose from 23 to 37% between 2015 and 2018, while past year of methamphetamine use among people using prescription opioids increased from 5 to 8% over this period (2). Among people reporting past-month heroin use, past-month methamphetamine use increased from 9 to 30% between 2015 and 2017 (3). Fifty Percent of a 2015 sample of people who inject drugs reported injecting both heroin and methamphetamine (4).

Drug overdoses, both fatal and non-fatal, now include increasing numbers of individuals who use both opioids and stimulants (5, 6). Opioid users experience adverse features that are even more prevalent in opioid + stimulant co-users. Co-users have higher prevalence of injection drug use, serious mental illness, hepatitis B or C (7) emergency department visits, days hospitalized, utilization of social services, involvement with the criminal justice system (8) as well as overdose (4, 6).

Treatment

Such consequences are among the reasons that many individuals with opioid or opioid + stimulant use disorders attempt to quit. More than 750,000, 560,000, 490,000 and 118,000 Americans seek treatment for disorders of use of heroin, amphetamines, cocaine and "stimulants" annually, respectively.[5] Agonist-like, antagonist and other therapeutics for opioid use disorders provide benefits but remain suboptimal for many for reasons that include variable adherence to these regimens (9, 10). More than 300,000 and 175,000 Americans receive methadone or buprenorphine annually, respectively;[6] about 20,000 receive naltrexone.

Despite available treatments, relapses (especially early in treatment) are frequent. Relapse occurred within a week in 59% of a group of individuals seeking to quit opioid use (11) and within a month in 37% of a group of individuals seeking to quit methamphetamine use (12). Rates of relapse decline during subsequent periods.

Current FDA approved agonist and antagonist therapies for opioid use disorder remain suboptimal for many. There are no FDA-approved medications for preventing disorders of use of opioids or stimulants, none for treating stimulant abuse disorders and none approved for disorders of combined opioid + stimulant use.

Prevention and treatment

Prevention

Pharmacologic strategies to *prevent* development of substance use disorders in those who are prescribed opioids or stimulants could reasonably focus on goals that include reducing the abuse liability of these substances while maintaining their therapeutic benefits for indications that include reductions in pain, symptoms of restless leg syndrome (RLS), symptoms of attention deficit-hyperactivity disorder (ADHD) and the daytime sleepiness of narcolepsy.

Animal model data

Tests in experimental animals and humans can evaluate abuse liability with sufficient reliability that they are used to place new substances in the appropriate regulatory schedule (13, 14). There are good animal models for several types of pain that are often validated in humans (15). Although animal models for ADHD or RLS are perhaps not as well validated (16, 17), there is still reasonably good ability to identify compounds that reduce abuse liability of opioid analgesics and stimulants while preserving many likely therapeutic benefits. Such identification in animal models can lead to assessments of such selectivity in human laboratory studies that test aspects of human abuse liability (14). Taken together, human and animal data that indicate lower abuse liability might support less restrictive scheduling of combined stimulant + agent that reduces abuse liability and/or opioid + agent that reduces abuse liability. Below, I consider some of the hurdles that a candidate antiaddiction therapeutic, pentilludin, might need to clear to be used in these contexts. Our discussion overlaps with recent work considering different "endpoints" for antiaddiction therapeutics (18–23) but approaches this topic in a different way (e.g., from the perspective of a novel agent's development).

1 https://clincalc.com/drugstats/drugs/amphetamine

2 https://www.samhas.gov/data/data-we-collect/teds-treatment-episode-data-set

3 https://www.cdc.gov/drugoverdose/rxrate-maps/index.html

4 https://www.hhs.gov/opioids/statistics/index.html; https://nida.nih.gov/research-topics/opioids

5 https://samhsa.gov/data/release/2020-national-survey-drug-use-health-nsduh-release

6 https://samhsa.gov/data/data-we-collect/n-ssats-national-survey-substance-abuse-treatment-services

Treatment

Pharmacologic strategies for treatment include facilitating initial abstinence, often in the face of withdrawal symptoms. Sustaining abstinence often requires success in the face of pharmacologic and behavioral effects of "lapse" doses of an abused substance as well as behavioral effects of exposures to stimuli that have been strongly associated with prior drug experiences (24). Current animal models cover some of these features (25). Studies of behavioral components of reinstatement triggered by experimenter-administered drug doses, pain or stress provide significant data (26–28). Below, I consider the hurdles that pentilludin would need to clear for use in reducing the reinstatement-promoting effects of lapse doses of stimulants or opioids and contrast this with hurdles required for less-targeted use in other aspects required to achieve and sustain abstinence.

A number of recent publications note interest in using reductions in use and/or quantity frequency as an indication for treatments for stimulant use disorders (18–22). I thus also consider the hurdles that pentilludin would need to clear should similar consensus develop *re* endpoints of reduced use in individuals with disorders of use of stimulants, opioids or stimulants + opioids.

PTPRD and pentilludin

PTPRD's phosphatase as a target for novel antiaddiction therapeutics

PTPRD, the receptor type protein tyrosine phosphatase D, is now a strongly-supported target for antiaddiction medication based on human, mouse model and *in vitro* data. Human genetic results (29) associate common variation in PTPRD with vulnerability to develop a substance use disorder [e.g., polysubstance (30–32), opioid (33), alcohol (34)]. PTPRD variation is also associated with the abilities to quit (smoking (35, 36), use of opioids (37) and alcohol when aided by naltrexone [though not acamprosate (38)]. There are PTPRD associations with individual differences in a specific constellation of rewarding responses to amphetamine administration (39).

PTPRD is a highly-expressed, largely-neuronal, substantially synaptic, single transmembrane protein (Figure 1) that (likely) transduces signals from binding to extracellular ligands (40) to alter activity of its intracellular phosphatase (41). Synaptosomal proteomic, *in situ* hybridization, single cell RNAseq and electron and light microscopic immuohistochemical data support these conclusions *re* localization (42–44).[7] Reported PTPRD extracellular binding partners include slit/trk, interleukin-1 receptor like and accessory proteins, synaptic adhesion-like molecules (SALMs) and the peptide asprosin (45–50). Substrates for PTPRD's phosphatase include proteins that regulate synaptic strength and maturation (51). Processes of PTPRD-expressing neurons grow when their PTPRD makes homomeric bonds with PTPRD expressed by adjacent cells (52). Cerebral cortical, ventral midbrain, striatal/ accumbens, reticular thalamic and other circuits that express PTPRD mRNA in likely glutamatergic, GABAergic, cholinergic and dopaminergic neurons are likely to develop and adapt differently when they express PTPRD at differing levels (53).

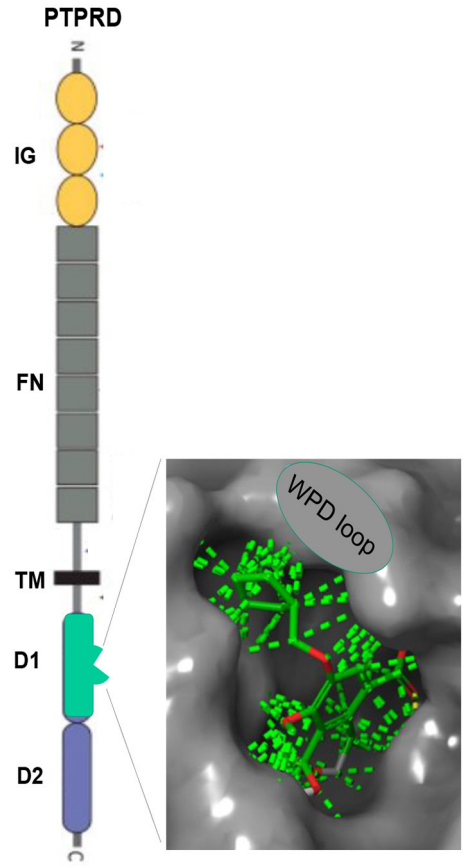

FIGURE 1
PTPRD. Extracellular immunoglobulin (IG) and fibronectin (FN) domains, transmembrane (TM) domain, D1 intracellular phosphatase domain. *Enlargement:* Pentilludin (NHB1109) bound to PTPRD phosphatase catalytic site and WPD loop. Dashed lines: van der Walls interactions.

Results from mouse models of common human allelic PTPRD variation

We have identified robust, 60- 70% individual differences in brain levels of expression of PTPRD mRNA (54) from human subjects with major vs. minor PTPRD SNP alleles. By contrast, PTPRD lacks common missense variants (53).

PTPRD knockout mice with only one wildtype gene copy and 50% constitutive alterations in levels of PTPRD expression (e.g., heterozygotes) thus model effects of common human PTPRD allelic variation. These mice are similar to wildtype littermates in tests of nociception (hotplate, tailflick), memory (Morris water maze), fear/anxiety (dark box emergence, thigmotaxis) and motor abilities (screen hang time, locomotion, rotarod) (54).

Mice with reduced PTPRD expression display sizable reductions in stimulant reward as assessed by conditioned place preference (CPP, 10 mg/kg cocaine) or self-administration (55).

7 https://mouse.brain-map.org

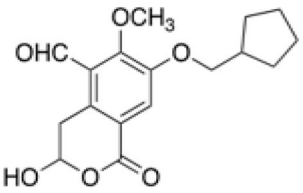

FIGURE 2
Pentilludin (NHB1109).

Results from synthesis and testing of 7-BIA and 70 novel analogs identification of pentilludin (NHB1109)

Despite concerns that phosphatases were "undruggable" (56), we reported a lead compound PTPRD phosphatase inhibitor, 7-BIA, in 2018 (55). We followed this discovery with further structure-activity work testing more than 70 analogs. We identified 10 congeners with greater potency than 7-BIA and several that are more selective (57).

NHB1109, which I now name pentilludin, is a 7-position substituted cyclopentyl analog that, like 7-BIA, appears to provide pseudoirreversible inhibition of PTPRD's phosphatase (Figure 2) (57). It displays more potency and more selectivity vs. 7-BIA with respect to both close family members (PTPRS and PTPRF) and other phosphatases at which 7-BIA displays some potency, including PTPRJ and PTPN1/PTP1B. IC_{50} values are $\geq 10^{-4}$ M at 12 other receptor- and non-receptor type protein tyrosine phosphatases tested and $\geq 10^{-5}$ M in EUROFINS screen for targets of current drugs.

Initial hurdles for pentilludin (NHB1109)

Pentilludin has cleared many initial hurdles in addition to the *in vitro* specificity noted above. Dose limiting toxicity comes from doses >10 x those that reduce cocaine reward. Mice treated daily with 200- 2,000 mg/kg gavage doses reduce food/water intake over serval days and lose weight (57). These results fit with recent observations that PTPRD's phosphatase serves as a receptor for the orexigenic actions of a "positive feedback" signal from fat cells, asprosin (50).

Initial effects of pentilludin (NHB1109) pretreatments on stimulant and opioid reward

Pentilludin has replicated and extended the reward-reducing effects of acute PTPRD phosphatase inhibition displayed by our initial lead compound PTPRD phosphatase inhibitor 7-BIA (55).

The lack of deal-breaking toxicities and the presence of evidence for reduced stimulant reward suggest that pentilludin has cleared significant hurdles and encouraged us to move forward with its development as an antiaddiction compound.

Evidence bearing on hurdles for development as an antiaddiction therapeutic

Selecting the appropriate next hurdles for pentilludin

Development of novel small molecules for use in clinical addiction-related contexts requires substantial good laboratory practice (GLP) studies to seek evidence for toxicities investigational new drug application (IND), first doses in human research volunteers, repeated doses in humans, and dosing in humans along with addictive substance doses.

For purposes of this article, I focus on the ways in pentilludin or any other reward-reducing pharmacotherapeutic might be developed and deployed in light of the regulatory and other hurdles that these pathways place before its development. Another frame for this discussion: what useful endpoints might be most appropriately targeted by the actions that I believe PTPRD phosphatase inhibitors will provide? Prior to this discussion, I return to details of genetic and other evidence that might provide clues to which subsequent hurdles pentilludin might face with the most confidence, *a priori*.

Some details from human evidence

Reevaluating details of selected human genetic studies supports testable hypotheses concerning the likely clinical influences of inhibitors that reduce the effects mediated by PTPRD. I evaluate these ideas in the context of the associations of common PTPRD haplotypes with substantial individual differences in levels of brain PTPRD expression (54).

Stimulant reward

Hart et al. provided a clinical composite "factor 1" derived from responses of genotyped research volunteers as they experienced the effects of 10 mg oral amphetamine doses in a laboratory setting (39). Factor 1 came from sparse factor analyses of responses to items on the Profile of Mood States, Drug Effects Questionnaire and Addiction Research Center Inventory questionnaires. These authors generously confirmed to us that their 9p genomic association with factor 1 identified PTPRD. Pharmacologic reductions in PTPRD activity are thus likely to reduce "factor 1" effects of amphetamine in a) increasing friendliness, elation, vigor, feel high, want more, like, amphetamine-like, benzedrine-like, marijuana-like and morphine/benzedrine group-like responses and b) decreasing ratings of depression, fatigue, confusion and pentobarbitol-chlorpromazine-alcohol group sedation.

Ability to quit use of addictive substances from different classes

The settings in which ability to reduce or quit substance use has been associated with variation in PTPRD may also provide clues. We identified polygenic association of PTPRD variation

with biochemically-confirmed success in smoking cessation in participants in three clinical trials aided by nicotine replacement or bupropion (36), in a trial aided by denicotinized cigarettes (58), in a trial aided by precessation nicotine replacement (59) and in a nicotine replacement community trial (60). We also identified PTPRD associations in comparisons of former vs. current smokers (58). Cox et al. identified PTPRD associations in comparisons of individuals who displayed lifetime opioid dependence diagnoses and who (a) self-reported abstinence >1 year vs. (b) continued to use (e.g., any abstinence <6 mos) (37). Biernacka et al. evaluated data from studies of pharmacologic effects on alcohol abstinence and identified robust PTPRD associations with time to relapse and time to relapse to heavy drinking in analyses of data from naltrexone treated subjects, though not in analyses of subjects treated with acamprosate (38). Interestingly, naltrexone responsiveness has been associated with drinking associated with reward seeking, while acamprosate responsiveness has been associated with drinking to seek relief from negative affect (61). These alcohol results, combined with data from smoking cessation and ability to quit opioid use, are consistent with the idea that antiaddiction agents that reduce PTPRD activity should aid reduction in use and/or abstinence from addictive substances of several classes.

Vulnerability to develop a substance use disorder of several classes

Vulnerability to develop a substance use disorder has been repeatedly associated with genomic variants at the PTPRD locus, beginning with our initial identification of a SNP in this chromosomal region using 10,000 SNP microarrays (30). We found PTPRD associations in comparisons of amphetamine dependent subjects to matched controls (62), research volunteers dependent on at least one illicit substance vs. corecruited or convenience controls (32, 63) and in more population- representative samples (64, 65). There are PTPRD copy number variant associations with vulnerability to develop opioid dependence (33). Agents that reduce PTPRD activity might thus be able to reduce development of dependence on addictive substances with which they were coadministered.

Evidence against toxicities

There is also human evidence that speaks to the likelihood that pharmacologically-modified effects mediated by PTPRD would be oncogenic or provide irreversible toxicities. Several papers term PTPRD a "tumor suppressor" gene based on e.g., its abilities to alter cancer-related phosphorylation pathways (66). However, PTPRD variation has not been reproducibly associated with any common cancer in genetic association studies [bladder (67), breast (68), colon (69), endometrial (70), kidney (71), leukemia (72), liver (73), lung (74), melanoma (75), non-Hodgkin lymphomas [e.g., (76)], pancreatic (77), prostate (78) or thyroid (79)]. Mice with reduced PTPRD expression fail to develop tumors at ages up to 24 mos. Carcinogenicity risks of agents that alter PTPRD seem unlikely to be greater than those of agents that influence any novel target.

There is also evidence from accidental human ingestions of Jack o'lantern mushrooms (*Omphalotus illudens*) (80, 81). These mushrooms contain the illudalic acid compounds that have activities at PTPRD-related phosphatases and provide the core of pentilludin's structure (82). They also contain compounds with muscarinic cholinergic activities (83). There has been no lethality or persisting sequelae noted after > 60 reported cases of accidental ingestion of these mushrooms. The ingestions do produce nausea/emesis. These symptoms have been attributed to the mushrooms' muscarinic effects by authors including a physician who ingested them (81). It is also possible that pentilludin, especially at high doses, will act at PTPRD to produce anorexia/nausea in humans. PTPRD is expressed in the arcuate hypothalamic neurons that express the orexigenic agouti related peptide AgRP (50) as well as in human enteric neurons (84) and in brainstem sites of cholinergic inputs to the cervical ganglia that innervate the stomach and small intestine. We have identified reduced food intake in mice treated with single doses of pentilludin that are >10 times higher than those that reduce cocaine and opioid reward (57). Data from accidental human Ingestions of *Omphalotus illudens* do provide evidence for the lack of other idiosyncratic human responses to illudalic acid doses that is likely to be pertinent for the illudalic acid analog pentilludin.

Human evidence limitations

The cumulative likelihood that all of the nominally-significant genetic associations cited above is due to chance is exceedingly small. When combined with the compelling mouse model and pharmacologic data, the *a posteriori* probabilities that PTPRD associations are due to chance are even lower. Nevertheless, none of these individual associations reproducibly meet the ultraconservative $p<10^{-8}$ Bonferroni corrected p-value required to declare "genome wide significance". The PTPRD SNPs or copy number variants that provide these associations are not the same across all studies. All studies of addiction genetics do not identify PTPRD. The size of these human associations also provides a caution: the effects of common PTPRD genomic variation are likely to be modest when compared to the cumulative effects of other genetic and environmental variation on individual differences in vulnerability to develop a substance use disorder, reward from administration of addictive substances or ability to reduce use/abstain from use.

All in all, with the human genetic, mouse genetic and human mushroom experience, cited above we thus have substantial confidence that "on target" pentilludin actions at PTPRD are likely to be well tolerated at the proposed therapeutic doses, with an acceptable therapeutic index.

Synthesis of human and animal evidence

The large effects on stimulant reward observed in our animal model studies (55), when we control other genetic and environmental features, suggest that both genetic and pharmacologic modulation of PTPRD activities can display robust effects. We thus seek

a developmental pathway for the PTPRD phosphatase inhibitor pentilludin on which we can demonstrate clinical benefits in a setting in which these benefits will be less likely to be obscured by the effects of variation in other genetic and environmental influences.

Pragmatically, we wish to select the hurdles that pentilludin will be most likely to clear during further development with the support that is available to us. Another way to frame this: we need to select the most appropriate endpoint for pentilludin's initial use. We provide several possible examples below.

Hurdles for development of antiaddiction therapeutic in several contexts

Potentially-modest hurdle: Reducing reward from "lapse" doses of stimulants during the initial period of abstinence

Reward from "lapse" doses of stimulants is likely to contribute to the reasons why relapse is so frequent when individuals with stimulant use disorders attempt to quit. A relapse occurred within a month in 37% of a group of individuals seeking to quit methamphetamine use (12). Rates of relapse decline during subsequent periods. Interventions that reduce the reward from "lapse" doses of stimulants taken during the key 1st weeks of a quit attempt could thus reduce relapse rates and aid longer term abstinence. Quantitative tests can biochemically confirm abstinence, exposure to modest "lapse" doses or relapse in appropriately-collected urine samples (85, 86). In this context, endpoints could be both (1) number of positive urine tests and (2) number of strikingly positive tests indicative of relapse in individuals who have previously displayed a modest positive indicative of lapse dosing.

"Lapse" is perhaps best defined in the smoking field, where smoking a single experimenter-administered cigarette can more than double the risk of continued smoking within the next 24 h (87). Such human evidence is complemented by animal studies that document how robustly experimenter-administered "priming" doses increase subsequent relapse-like efforts to self-administer drugs during periods of "abstinence" (28). Reducing the reward from "lapse" stimulant doses taken during the 1st week of attempted stimulant abstinence should thus provide a significant benefit for individuals seeking to quit use of stimulants.

IND-enabling studies for development of pentilludin to reduce reward from "lapse" doses of stimulants during the initial period of abstinence could be relatively tractable. Several weeks' pentilludin dosing in two species could be coupled with simulated "lapse" doses of stimulants. Since there are likely fewer than 200,000 individuals treated with any pharmacological adjunct to aid abstinence from a stimulant use disorder[8] in the US, use of pentilludin to aid abstinence by reducing the reward from lapse doses of stimulants sampled during the 1st week of abstinence might even provide an "orphan" indication. Achieving orphan designation could encourage commercial partnerships to continue development by providing tax benefits and a period of exclusivity.[9]

The benefits of tractable IND-enabling work, possible orphan indication, ability to biochemically confirm both lapse dosing and abstinence and a plausible link to the reward conferred by stimulants appears to raise only moderately-high hurdles to development of pentilludin for this indication. However, this indication would target a market of only modest size. We do not have a clear indication of the fraction of the total variance in relapse to stimulant use that comes from PTPRD-sensitive stimulant reward during lapse doses vs. the fraction that comes from other genetic and environmental variables. The hurdle provided by this indication for pentilludin may thus be higher than we anticipate, *a priori*.

Potentially-higher hurdle: Reducing abuse liability from prescribed stimulants and/or opioids

Prevention of the substance use disorders that arise from use of prescribed drugs would provide a large clinical impact. This impact could come from strategies that reduced the reward that these prescribed drugs provide while maintaining their therapeutic benefits. A practical manifestation of this impact could be lower scheduling of combination products (e.g., pentilludin + stimulant or pentilludin + opioid).

Human laboratory and experimental animal assessments of reward have been key to Drug Enforcement Administration (DEA) assignment of appropriate regulatory schedules to new drugs (Box 1[10]), with consultation by FDA (13). Postmarketing data identifying frequencies of missuse and abuse in the community add valuable information (13). Possible endpoints in this developmental pathway would be demonstration of lower signs of abuse liability in standard testing paradigms and thus reduced scheduling for combination products.

One set of hurdles for developing pentilludin for use in this context relates to the magnitude of its effects: could co-administration of pentilludin with a Schedule II stimulant or opioid reduce abuse liability sufficiently to allow the combination product to be marketed as Schedule III? It is fortunate that we do have genetic association of PTPRD variation with individual differences in rewarding responses to laboratory-administered amphetamine doses (*noted above*). Assessments using many of the same instruments has provided data that has been accepted by regulatory agencies to schedule new drugs in the past.[11]

Another set of hurdles results from the chronicity of treatment: can IND-enabling and other studies adequately reflect the years-long patterns of use of prescribed stimulants and, for some, opioids?

An additional hurdle come from the differences in pharmacodynamic properties of pentilludin (a pseudoirreversible agent with an apparent days-long physiological half-life) vs. those of e.g., amphetamine or oxycodone, with shorter physiological half-lives.

8 https://www.samhas.gov/data/data-we-collect/teds-treatment-episode-data-set

9 https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products

10 https://www.dea.gov/drug-information/drug-scheduling

11 https://www.fda.gov/media/116739/download

BOX 1 Schedules for controlled substances.

Schedule I: Drugs with no currently accepted medical use and a high potential for abuse. (ex: heroin, LSD, marijuana (cannabis), 3,4-methylenedioxy-methamphetamine (ecstasy), methaqualone, peyote.

Schedule II: Drugs with a high potential for abuse, potentially leading to severe psychological or physical dependence, that are considered dangerous. (ex: combination products with <15 mg hydrocodone per dosage, cocaine, methamphetamine, amphetamine, methadone, hydromorphone, meperidine, oxycodone, fentanyl, methylphenidate.

Schedule III: Drugs with a moderate to low potential for physical and psychological dependence, less than Schedule I/ II drugs but more than Schedule IV. (ex: products containing < 90 mg codeine per dosage, ketamine, anabolic steroids, testosterone.

Schedule IV: Drugs with a low potential for abuse and low risk of dependence. (ex: diazepam, tramadol, alprazolam, carisoprodol, propoxyphene, lorazepam, pentazocine, zolpidem).

Schedule V: Drugs with lower potential for abuse than Schedule IV, many containing limited quantities of certain narcotics and often used for antidiarrheal, antitussive, and analgesic purposes. (ex: cough preparations with <200 mg codeine/100 ml, diphenoxylate/atropine, difenoxin/atropine, pregabalin, attapulgite).

Producing a robust abuse-resistant combination formulation that deters extraction of the opioid or stimulant provides another hurdle.

And, finally, assuring that combination formulations retain human benefits in reducing pain, combatting ADHD or RLS symptoms or reducing daytime sleepiness of narcoleptics provides a significant hurdle as well.

Despite these hurdles, the potential for preventing development of substance use disorders by marketing pentilludin-containing stimulant and opioid combination products with reduced abuse liability and correspondingly-less restrictive scheduling remains a powerfully attractive idea. Such marketing would then have to clear a final hurdle: Real world post marketing surveillance data that demonstrated less abuse (13).

Potentially-higher hurdle: Aiding initiation and maintenance of abstinence in individuals with ongoing stimulant or opioid use disorders

Established disorders of stimulant and opioid use are likely to be maintained by complex polygenic genetic and environmental factors.[12] A pharmacologic "magic bullet" that could arrest such ongoing disorders without unacceptable side effects in all abusers would provide huge societal benefits and has therefore been sought. However, the complex interplay of habitual and learned behaviors with the pulls exerted by both pharmacological reward and reduction in withdrawal's aversive features provides a daunting hurdle for any antiaddiction pharmaceutic to clear.

One conceptual approach to this "magic bullet" thinking considers the different ways in which individuals with substance use disorders might sustain their use and thus come to treatment *via* different pathways. Studies of alcohol use disorders have sought to separate drinkers who largely drink for the reward that alcohol provides and those who largely drink to mitigate negative features of their lives and affects (88). As noted above, these studies have identified more prominent benefits of naltrexone for those who drink to experience reward and more benefits of acamprosate for those who drink to reduce negative affect and feelings. PTPRD variants provide strong association with ability to reduce alcohol use with naltrexone, without any evidence for a strong or even moderate-strength association with ability to reduce alcohol use with acamprosate (38). PTPRD effects could thus plausibly be more prominent in aiding reductions in or abstinence from stimulants or opioids in the subset of individuals whose use was the most strongly maintained by the reward that they obtain from these substances. Possible endpoints for this approach could include reduced or absent urinary levels of abused substances in unselected treatment-seeking substance users. Another endpoint could focus on the individuals whose substance use disorders had been most maintained by the rewarding effects of the substance.

Hurdles to development of pentilludin to aid initiation of and/or maintenance of reductions in or abstinence from use of addictive substances are thus daunting, but perhaps not impossible. In an ideal scenario, drug addiction investigators would identify the stimulant or opioid users whose use was most dependent on the reward that these drugs provide vs. habitual use or use to relieve negative features. In an even more ideal scenario, drug addiction investigators would also provide solid data (*re* benefits) that would lower barriers to licensing novel agents based on reductions in use of addictive drugs rather that complete abstinence. In such a setting, one of the highest hurdles to testing pentilludin to aid initiation of reduced use/abstinence in the most reward-dependent users might be studies identifying little pentilludin toxicity with co-use of the multiple addictive substance that are characteristic of many with substance use disorders. Aid in maintaining abstinence, once achieved, could be analogous to reducing reward from "lapse" doses, as noted above. Hurdles to aiding initiation and maintenance of abstinence in individuals with the most reward-dependent ongoing stimulant or opioid use disorders thus might not be as high as they appeared *a priori*.

Conclusions

Congressional recognition of the need for pharmacotherapeutics for prevention and treatment of substance use disorders and the difficulties of such development led to establishment of the medications development program at the National Institute on Drug Abuse in 1990, and to its increasing funding and sophistication during subsequent years.[13] Bases for regulation of substances with abuse liability dates to the early 1900's and currently centers on the Controlled Substance Act and related legislation.[14] Despite this regulatory sophistication and support for medication development, there is still no

12 https://nida.nih.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction

13 https://nida.nih.gov/about-nida/organization/divisions/division-therapetics-medical-consesquences-dtmc/research-programs

14 https://uscode.house.gov/view.xhtml?path=/prelim@title21/chapter13&edition=prelim

licensed pharmacotherapeutic that can prevent development of substance use disorders in those who are prescribed stimulants or opioids and none that can effectively treat established stimulant use disorders.

In these contexts, development of pentilludin, a novel pharmacotherapeutic that acts at a novel addiction-associated site to reduce reward from stimulants and opioids, provides an example of the promises and hurdles that face antiaddiction medication development. Categorizing pentilludin's strengths and limitations in several potential settings and with several different sets of endpoints outlines some of the ways in which choosing the correct set of hurdles and endpoints could increase the likelihood that this compound will be able to reach general clinical use.

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

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Conflict of interest

VA intellectual property covering pentilludin with GU as a coinventor.

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Evaluating longitudinal relationships between parental monitoring and substance use in a multi-year, intensive longitudinal study of 670 adolescent twins

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Introduction: Parental monitoring is a key intervention target for adolescent substance use, however this practice is largely supported by causally uninformative cross-sectional or sparse-longitudinal observational research designs.

Methods: We therefore evaluated relationships between adolescent substance use (assessed weekly) and parental monitoring (assessed every two months) in 670 adolescent twins for two years. This allowed us to assess how individual-level parental monitoring and substance use trajectories were related and, via the twin design, to quantify genetic and environmental contributions to these relationships. Furthermore, we attempted to devise additional measures of parental monitoring by collecting quasi-continuous GPS locations and calculating a) time spent at home between midnight and 5am and b) time spent at school between 8am-3pm.

Results: ACE-decomposed latent growth models found alcohol and cannabis use increased with age while parental monitoring, time at home, and time at school decreased. Baseline alcohol and cannabis use were correlated (r=.65) and associated with baseline parental monitoring (r=−.24 to −.29) but not with baseline GPS measures (r=−.06 to −.16). Longitudinally, changes in substance use and parental monitoring were not significantly correlated. Geospatial measures were largely unrelated to parental monitoring, though changes in cannabis use and time at home were highly correlated (r = −.53 to −.90), with genetic correlations suggesting their relationship was substantially genetically mediated. Due to power constraints, ACE estimates and biometric correlations were imprecisely estimated. Most of the substance use and parental monitoring phenotypes were substantially heritable, but genetic correlations between them were not significantly different from 0.

Discussion: Overall, we found developmental changes in each phenotype, baseline correlations between substance use and parental monitoring, co-occurring changes and mutual genetic influences for time at home and cannabis use, and substantial

genetic influences on many substance use and parental monitoring phenotypes. However, our geospatial variables were mostly unrelated to parental monitoring, suggesting they poorly measured this construct. Furthermore, though we did not detect evidence of genetic confounding, changes in parental monitoring and substance use were not significantly correlated, suggesting that, at least in community samples of mid-to-late adolescents, the two may not be causally related.

KEYWORDS

cannabis, alcohol, adolescence, GPS, parental monitoring, behavioral genetics, intensive longitudinal assessment

1. Introduction

Adolescence is a time of rapid psychological, developmental, and environmental change that is frequently characterized by increases in autonomy, exploration, and risk-taking behaviors (1). Correspondingly, many youths begin to experiment with drugs and alcohol during this period (2). A majority of late adolescents report that alcohol and cannabis are easily obtainable as their use is often culturally sanctioned and, in many US states, they can be legally obtained by slightly-older peers (3, 4). Along with these clear environmental influences on the availability of addictive substances, individual differences in adolescent substance use are also influenced by genetic factors (5, 6).

While developmentally normative in United States adolescents (3), substance use places youth at increased risk for a multitude of adverse consequences. Adverse outcomes include long term health consequences like increased risk for cardiovascular diseases, cancers, and future substance use disorders, as well as more immediate consequences like physical injuries, impaired judgment, risky sexual behaviors, legal consequences, and even accidental death (7, 8).

To protect against these risks, numerous behavioral interventions have been developed to prevent or reduce adolescent substance use. Parent management training programs, such as Parent Management Training—Oregon Model (PMTO), are among the most popular of these interventions (9, 10). These interventions are premised on the coercion model of delinquency, in which parents who initially adopt harsh or coercive parenting practices evoke problem behaviors from their children and subsequently respond to these behavior problems by disengaging from supervising their children (9). The combination of these evoked behavior problems and subsequent decreases in parental monitoring are then hypothesized to promote further delinquent behaviors, like engaging in substance use. PMTO programs therefore attempt to pre-empt this trajectory by intervening to foster more positive parent–child interactions and to increase parental monitoring of children's activities. Such programs have proven to be reasonably effective in reducing adolescent substance use, with recent meta-analytic estimates suggesting a small to moderate effect of parent management training on adolescent substance use (10). Furthermore, several studies report robust negative associations between parental monitoring and adolescent substance use, with several showing longitudinal associations wherein parental monitoring in childhood and adolescence predicted substance use in emerging adulthood (11–13).

However, this conceptualization of parental monitoring has been challenged by subsequent research. While early conceptualizations of the relationship between parental knowledge and substance use posited that the relationship represented the effects of parental surveillance or control of adolescent activities on reducing delinquent behavior (14), a series of studies by Kerr and Stattin on the relationship between parental monitoring and delinquency in Swedish youth demonstrated that adolescents' willingness to disclose information about their activities to their parents was more predictive of both parental knowledge and subsequent delinquency than were active parental surveillance efforts (15–18). Furthermore, Eaton et al. found that the relationship between both parental knowledge and adolescent disclosure was largely accounted for by adolescent personality, suggesting that pre-existing differences in adolescent personality, such as one's willingness to disclose information to their parents, explain previously observed relationships between parental monitoring and delinquent behaviors.

Additionally, studies supporting the relationship between parental monitoring and delinquent behaviors like substance use universally rely on correlational research designs conducted in cross sectional or sparse longitudinal data. Such designs are poorly suited to the causal claims inferred from them, as a correlation may arise from a causal relationship between two variables, but it may also be due to any number of other factors influencing both variables (19, 20). An additional complication is that commonly assessed, putatively environmental risk factors for behavioral traits are often heritable themselves (21). This highlights the importance of gene–environment correlation, where heritable attributes of individuals affect the environmental experiences they have. Genetically informed research designs have often found that relationships between alleged environmental risk factors and behavioral outcomes are largely explained by pre-existing impacts of genetics (22). In the case of parental monitoring, Eaton et al.'s finding that correlations between parental monitoring and substance use appear to be largely attributable to adolescent personality traits, is suggestive that their relationship could reflect gene–environment correlation, wherein genes influencing substance use also influence the degree of parental monitoring one experiences. For example, adolescent control, a highly heritable personality trait, may have led to both increased parental disclosure and reduced substance use, thereby confounding the correlation between parental monitoring and substance use. Such findings highlight the role of gene–environment correlations in the relationship between behavioral traits and hypothesized environmental risk factors, necessitating the use of genetically informative samples to measure and control for these confounds.

Furthermore, parental monitoring, like other environmental risk factors for behavioral outcomes, is traditionally assessed via

self-report. Such questionnaires can be effective, but limitations exist over and above issues such as recall bias (23). Ambulatory assessment using wireless devices—typically smartphones—represent a newer and relatively untested approach to evaluating behaviors or environmental exposures quasi-continuously over time (24). Questionnaires can be administered on the device at any time and any interval. Additional "passive" data can be collected on a participant's location, movement and, depending on the sensors available, biological attributes such as cardiovascular or respiratory function (25). These technological developments may facilitate novel measurement paradigms to supplement or even replace self-report inventories (26), but, while preliminary research has been promising (25, 27), the feasibility of passively collecting valid and useful psychological data is less clear.

We thus attempted to address some of these challenges using data from the CoTwins sample, an ongoing intensive longitudinal twin study of adolescent substance use conducted at the University of Colorado and the University of Minnesota. In the CoTwins study, 670 twins and their parents were assessed in-person at an intake assessment, at which time an app was installed on each twin's smartphone. They were then assessed remotely via the smartphone app for 2 years. We used the app to administer regular questionnaires including measures of alcohol use, cannabis use, and parental monitoring. The app also passively monitored geographical location, which we used to infer whether an individual was at home or at school during days/times when one would expect an adolescent to be at home or at school. We hypothesized that these geospatial measures would measure discordance between a twin's actual and expected location during these hours and would thus offer additional information on the parental monitoring construct. Parents of adolescents who, for example, were frequently out of the home late at night or were away from school during school hours were hypothesized to have a lower degree of parental knowledge than parents of adolescents who were generally at home or at school during these times. Correspondingly, under the coercive model of parenting leveraged by some popular substance use interventions (9, 28), such adolescents would be expected to exhibit greater rates of delinquent behaviors like substance use.

These quasi-continuous locations were analyzed along with the questionnaire data to characterize adolescent change in these domains from ages 14 to 18. These data allowed us to (1) replicate the expected correlation between parental monitoring and substance use, (2) evaluate whether change in adolescent substance use is associated with change in parental monitoring during adolescence, (3) determine whether simple GPS-derived measures of location could serve as proxies for parental monitoring or environmental risk for substance use, and (4) using the genetically informative twin design, determine whether relationships between substance use and parental monitoring trajectories were confounded by mutual genetic influences.

In doing this, we offer a further test of the hypothesis that parental monitoring is causally related to adolescent behavioral problems like substance use. If changes in parental monitoring correspond with changes in substance use above and beyond what can be explained by genetic confounding effects, this study will bolster support for a possible causal relationship between them. However, if changes in parental monitoring correspond poorly with changes in substance use or if the relationship appears largely driven by gene–environment correlation, then evidence for a causal relationship between the two would be significantly challenged, as would the role of parental monitoring as a target in substance use interventions.

2. Materials and methods

2.1. Participants

Participants were adolescent twins who were recruited to participate in the CoTwins study in 2015 and 2016. These participants were recruited using the Colorado Twin Registry, a population-based registry of twins born in Colorado. Families were eligible if they had twin children between the ages of 14 and 17, who had Android or iOS smartphones, and who resided in Colorado or nearby states. The study was approved by the University of Colorado Boulder and University of Minnesota Institutional Review Boards.

Informed consent and assent were obtained from both parents and children. The sample consisted of 109 monozygotic (MZ) twin pairs (67 female and 42 male pairs) and 221 dizygotic (DZ) twin pairs (71 female, 63 male, and 87 opposite-sex pairs). Their ages at recruitment were between 14 and 17 (mean: 16.1; SD: 1.1); their race and ethnicities, as described by their parents, were 71% non-Hispanic white, 14% Hispanic/Latinx, 10% multi-racial, and 3% of other ethnicities. At the baseline visit, 73% of participants reported that their parents were still married while 27% reported a parental divorce. At the time of their first remote survey, 73% of twins reported living with both their mother and father, 5% reported an additional adult in the house, 5% reported living with at least one stepfather or stepmother, and 16% reported living with only one guardian: either their mother, father, or another adult.

2.2. Procedure

Following recruitment, we conducted an intake visit where the twins' zygosity was determined and twins and their parents completed baseline assessments including measures of parental monitoring and substance use. During the visit, the CoTwins software application (the "app") was installed on the twins' phones, for iOS and Android operating systems. The app was then used to regularly administer remote assessments to the twins, but not to their parents, for the duration of their participation in the study. Remote questionnaires were adapted from the in-person measures to help ensure comparability while minimizing participant burden. Data analyzed in this manuscript were collected by the app between May of 2015 and November of 2018. Initially, twins participated for 1 year of remote assessment via the app. Seventy-nine percent of twins agreed to a second year.

In addition to administering surveys, the app also collected global positioning system (GPS) latitude/longitude and time stamp data, with collection density/accuracy calibrated to guard against substantial battery drain. Android and iOS location modules are "black boxes," which perform sensor fusion and produce location estimates in unknown and proprietary ways. On iOS, we used the significant change location API and locations were recorded only when the user moved a "significant" distance and no more frequently than every 5 min. On Android, the user's location was recorded every 5 min. On an approximately weekly basis, study staff monitored questionnaire

completion rates and passive data collection and contacted twins to offer technical support when necessary. Before data cleaning, the median accuracy, as reported by the location API, was 65 m. After removing locations with an accuracy worse than 500 m, it was 17.1 m.

2.3. Measures

2.3.1. Substance use

Substance use questions were derived from the Substance Abuse and Addiction collection of the PhenX Toolkit, a set of reliable and well-validated substance-abuse related measures that have been made publicly available to improve the harmonization of substance use measurement across research studies (29, 30) though, due to low base rates of other substance use, only alcohol and cannabis use were included in subsequent analyses (30, 31). Past week alcohol use frequency was assessed by the question "In the last 7 days, since last [assessment date], on how many days did you drink any alcohol?" Alcohol quantity per use occasion was assessed via the question "On those days that you drank alcohol, how many drinks did you usually have each day? (One "drink" is equal to 1 can or bottle of beer, a glass of wine, or a shot of hard liquor.)"

Similarly, marijuana use frequency was measured by the item "In the last 7 days, since last [assessment date], on how many days did you use any marijuana or hashish, including smoking marijuana, edibles, vaping, dabbing, or however else you may have used marijuana?" Marijuana quantity, measured as the number of times per day a participant used marijuana on a typical day in which they used marijuana, was assessed via the question "On each day that you used marijuana (whether smoked, eaten, vaped, dabbed, or however it was used), how many times per day did you use enough to feel the effects?"

Substance use was assessed every 3–7 days (uniformly distributed with mean = 5) until May, 8th, 2017, roughly 2 years after the start of data collection, when the frequency was changed to 5–9 days (uniform with mean = 7) to further reduce participant burden. On average, participants completed 49.7% of substance use assessments which they were administered, completing an average of 62.1 assessments over the duration of the study. Weekly substance use quantity-frequency was calculated for alcohol (as drinks per week) and cannabis (as cannabis use occasions per week). These were then log-transformed (after adding 1 to keep zeros) to reduce the influence of outliers on model results and so that parameter estimates would represent relative changes rather than absolute changes in the outcome variable (32). Descriptive statistics, including ICCs and Cronbach's α's, for the substance use variables, parental monitoring and geospatial measures, are presented in Table 1.

2.3.2. Parental monitoring

As no measure of parental monitoring was available from the PhenX toolkit at the time of analysis, parental monitoring questions were obtained from a parental monitoring questionnaire developed by the Minnesota Center for Twin and Family Research (33, 34). Prior research using this questionnaire has established that both the parent and adolescent reported parental monitoring measures and their subscales are reliable and associated with related constructs like adolescent personality and delinquent behaviors (34). At baseline, parental monitoring was assessed along with parental solicitation (the extent to which parents ask about their children's activities) and parental disclosure (the degree to which adolescents share information about their activities) using a 15-item parental monitoring questionnaire, with twins completing the adolescent-report version and their parents completing an analogous parent-report version. To avoid artificial depression due to, for example, single parent families, the maximum values for each question (most knowledge of the child's activities) were chosen across all parental figures for that twin. Then, maximum values were summed across questions to produce a sum score. Questions on this form included items assessing the degree to which parents were aware of, solicited information on, or were told where and with whom adolescents spent their time.

The baseline measures of parental monitoring differed from the measure which were administered remotely to the adolescents after the baseline visit. Hence, these baseline measures of parental monitoring were not included in subsequent analyses of relationships between parental monitoring and substance use, except as a means of testing the validity of our remote parental monitoring measure. After the baseline visit, adolescent-reported parental monitoring was administered remotely using only the parental knowledge subscale from the in-person parental monitoring questionnaire. The parental knowledge items were chosen to represent the parental monitoring construct as parental knowledge has been found to be more predictive of adolescent substance use than either parental solicitation or adolescent disclosure, likely because it includes information parents have obtained through both processes (18, 34). These consisted of five items per parent/guardian. This questionnaire was administered to the twins randomly every 50–70 days (uniform with mean = 60). On average, participants completed 92.4% of remote parental monitoring assessments, completing an average of 9.1 assessments over the duration of the study. The five questions used to assess parental monitoring were (1) "My [parent] knows who I spend time with," (2) "My [parent] knows how I spend my money," (3) "My [parent] knows where I am most afternoons after school," (4) "My [parent] knows where I go at night," and (5) "My [parent] knows what I do with my free time." These items were rated on a five-point scale from "never" to "always." Twins were asked to respond to these five questions for each of the adult parental figures they lived with. As on the in-person assessment, parental monitoring scores were computed, by selecting the highest value on each item across all parental figures and summing these items to produce a sum score. These remote parental monitoring questions are included as a supplement to the manuscript.

At intake, adolescent-reported parental monitoring was highly correlated with adolescent-reported parental disclosure ($r = 0.72$) and moderately correlated with adolescent-reported parental solicitation ($r = 0.46$). Adolescent-reported monitoring was more modestly correlated with parent-reported monitoring ($r = 0.35$) and disclosure ($r = 0.22$) but was not correlated with parent-reported solicitation ($r = 0.00$). At intake, adolescent reported parental monitoring measures were reasonably reliable as individual subscales (Cronbach's alphas = 0.77–0.79) and when aggregated together (Cronbach's alpha = 0.86) suggesting these scales were measuring related constructs. Similarly, baseline parent-reported parental monitoring measures were also reliable both as individual scales (Cronbach's alphas = 0.83–0.86) and in aggregate (Cronbach's alpha = 0.86). Adolescent-reported parental knowledge and parental disclosure at baseline were both significantly correlated with alcohol ($rs = -0.13$ to

TABLE 1 Descriptive statistics of substance use, parental monitoring, and geospatial variables.

	Total responses	Mean responses per participant	Grand mean	Grand SD	Mean (aggregated within subjects)	SD (aggregated within subjects)	ICC	Cronbach's α
Alcoholic drinks per week	40,923	62.1	0.45	2.43	0.51	1.54	0.37 [0.35, 0.40]	0.97 [0.96: 0.98]
Marijuana uses per week	40,919	62.1	0.25	1.68	0.35	1.76	0.61 [0.58, 0.63]	0.98 [0.98: 0.99]
Parental monitoring	5,925	9.0	16.40	3.21	16.43	2.58	0.67 [0.65, 0.70]	0.92 [0.83: 0.87]
Time spent at home	14,872	40.2	0.63	0.30	0.67	0.19	0.33 [0.30, 0.37]	0.97 [0.96: 0.98]
Time spent at school	9,637	25.1	0.50	0.28	0.51	0.19	0.36 [0.33, 0.40]	0.94 [0.94: 0.96]

Total responses are the number of total observations recorded for a measure. Mean responses per participant are computed as the total number of responses divided by the number of contributing participants. Grand means and standard deviations (SDs) are the mean and standard deviation for each measure disaggregated across participants. The mean and SD aggregated within subjects are the mean and standard deviation for the measure after aggregating observations within subjects (i.e., computing within subject means). To ease interpretation, alcoholic drinks per week and marijuana uses per week are not presented on a log scale here, though they are log transformed within the models. Parental monitoring is measured as the sum of the items on the adolescent-reported parental monitoring questionnaire for the parent with the highest parental monitoring score at that timepoint. Time spent at home is defined as the proportion of time spent within 100 meters of one's home address between 12AM and 5AM on a given day, while time spent at school is defined as the proportion of time spent within 200m of a Colorado High School between 8AM and 3PM on a given day. Intraclass coefficients (ICC) are the single random raters ICC and measure the average correlation between pairs of observations on each measure. Cronbach's α are measured longitudinally, with each response representing an item in a "scale" comprising all of an individual's responses over the duration of the study.

−0.09) and marijuana use ($rs = -0.22$ to -0.20) at the first remote follow up while adolescent-reported parental solicitation was not significantly correlated with either substance use measure ($rs = -0.04$ to 0.00). Similarly, baseline parent-reported parental knowledge and adolescent disclosure were significantly correlated with first-follow-up alcohol ($rs = -0.18$ to -0.13) and marijuana use ($rs = -0.19$ to -0.29) while parent-reported solicitation efforts were only significantly associated with alcohol use ($r = 0.09$).

The rank correlation between the intake in-person parental monitoring assessment and the first remote follow-up assessment, approximately 1 month later, was 0.57 (95% CI = 0.48–0.61) for the adolescent-report form and 0.35 (95% CI = 0.28–0.41) for the parent-report form. Cronbach's alpha for the first remote follow-up parental monitoring score was 0.75 (95% CI = 0.72–0.78). Remote parental monitoring assessments had an intraclass correlation coefficient of 0.68, indicating moderate correspondence between repeated measures over time.

2.3.3. Geospatial measures

To facilitate analyses, prior to computing geospatial measures, each twin's GPS locations were first standardized into a series of consecutive, 30-min time windows, starting at their first recorded point and ending at their last recorded point. For each twin, the GPS location within each window closest to the center of that window was chosen to represent the window and produce a standardized point. Next, we accounted for the fact that the iOS application only records a point when the user has moved more than ~500 m, by filling forward missing standardized iOS points for up to 12 h. The 12 h period was chosen as a commonly expected duration with no movement, such as an over-night stay at home. On average, after data cleaning and fill-forward procedures, participant location was reported for at least part of the day on 76.2% of days, with at least one point recorded for 50% of possible 30-min windows for the duration of the study.

For estimates of time at home, a filled and standardized point was considered "at home" if it was within 100 m of any of the geocoded home addresses on file for that family. Then, the fraction of points at home between midnight and 5 AM was calculated each week, for each twin, and this fraction was used as the "time at home" variable. If a manual inspection showed that a twin was consistently never at home, we inferred that we had an incorrect home address and removed them from the at home data.

For time at school, a list of public and private schools in the state of Colorado was downloaded from the ElSi Table Generator maintained by the National Center for Education Statistics.[1] The latest relevant data release was used, from the 2015 to 2016 school year. High schools were selected, and the physical address of each school was geocoded. A filled and standardized point was considered "at school" if it was within 200 m of any of the schools in the list. Then, those points were subset to include only school hours (8 AM–3 PM) and school days, as determined by Colorado public school calendars and manual review of the location data. Time at school was then defined as the fraction of remaining points at school each week, for each twin. If a manual inspection showed that a twin was consistently never at school, we concluded that their school was not included in the ElSi database or that they were home schooled and set their time at school to missing.

2.3.4. Zygosity

Twin pairs were rated as either monozygotic (MZ), same sex dizygotic (DZ), or opposite sex dizygotic (OS). OS twins were automatically rated as dizygotic as there are no opposite sex MZ twins. For same sex twins, zygosity was determined by two expert coders, who independently assessed twin similarity on six physical traits on a five point similarity scale. Discrepancies between raters were resolved via discussion before arriving at a consensus zygosity determination.

2.4. Analyses

To characterize average longitudinal phenotypic trajectories (i.e., mean change during adolescence) for time at home, time at school,

1 https://nces.ed.gov/ccd/elsi/tableGenerator.aspx

parental monitoring, drinks per week, and cannabis uses per week, non-linear mean functions were estimated using generalized additive mixed models (GAMMs) fit by the R package gamm4 (35). The phenotype of interest was predicted by smooth functions of age, which were fit by penalized regression with sex as a covariate. The basis dimension for each phenotype was chosen using the residual randomization test implemented in the R package mgcv (36) with the random effects for each smooth term nested by twins within twin pairs.

To understand individual differences (i.e., variance) in the developmental trajectories of parental monitoring and substance use and to estimate the genetic and environmental contributions to these differences, we utilized a multivariate growth modeling approach. We expect that, after age 18, when many adolescents complete high school and leave the home, the meaning of the parental monitoring and geospatial phenotypes and their relationships to substance use will change. Therefore, to avoid these likely confounds, all assessments after age 18 were removed before fitting these multivariate latent growth models. The models were fit using the R package OpenMx (37, 38). Missing observations were addressed via full information maximum likelihood estimation.

To represent individualized developmental trajectories in each phenotype as a function of participant age, we considered structural equation models predicting each outcome as a function of a random intercept, random effect of age (slope), and random effect of age squared (acceleration). The inclusion of linear and quadratic age random effects was based on initial models run in the R package lme4 (39), where models with random intercepts and age slopes at both the individual and family level were compared to models with random intercepts, age slopes, and age quadratic terms. Cubic models were considered as well but were ultimately not selected due to those models failing to converge in lme4. Based on AIC and BIC criteria, models which included random age slopes and quadratic terms offered superior fit for all five phenotypes considered.

To render intercepts and slopes more interpretable, age and age^2 were scaled so that a value of 0 corresponded to age 14. To measure correlations between growth parameters (e.g., the correlation between the random alcohol slopes and random parental monitoring slopes) each model included two of the five measures under study (alcohol use, cannabis use, parental monitoring, time spent at home, and time spent at school). When jointly modeling substance use variables with parental monitoring, 10 total models were implemented, representing all possible combinations of these five outcomes.

To assess the additive genetic (A), shared environmental (C), and nonshared environmental (E) contributions to these growth parameters and the degree to which genetic and environmental influences are shared between growth parameters, we decomposed the random effects and residuals into ACE components. ACE models leverage the difference in genetic relatedness between MZ twins, who share 100% of segregating genes, and DZ twins, who share on average 50% of segregating genes, to estimate the genetic and environmental contributions to a phenotype (or the covariance between two phenotypes). Additive genetic effects (A) represent the influence of genetic variation on phenotypic variation and are identified when MZ twins are more alike than DZ twins. Shared environmental effects (C) represent elements of the environment that increase the similarity of twins in the same family and are identified when MZ twins are less than twice as phenotypically similar to one another as DZ twins (because MZ twins are twice as genetically similar as DZ twins, MZ twins are expected to be twice as similar as DZ twins in the absence of shared environmental influences). Non-shared environmental effects (E) represent elements of the environment that lead to differences between members of the same family and are identified when MZ twins are not perfectly correlated with one another.

Confidence intervals for the variances and covariances of the random intercepts, slopes, and quadratic terms and their ACE variance components were obtained using likelihood-based confidence intervals implemented in OpenMx. To provide readers with additional clarity on the structure of these models, an example path diagram of the model comparing drinks per week and parental monitoring is provided in Figure 1.

Together, these ten growth models were used to estimate a 15×15 ACE decomposed variance–covariance matrix of the random intercepts, slopes, and quadratic terms estimated in the models. Cross-phenotypic correlations between the random intercepts were used to measure whether variables were correlated at age 14 while those between the random slopes and quadratic terms measured whether developmental changes in a phenotype (e.g., parental monitoring) were associated with corresponding changes in another phenotype (e.g., substance use). The ACE decompositions of the variances were used to measure the genetic and environmental contributions to the initial levels and developmental changes in each phenotype, such as whether the development of parental monitoring or substance use is heritable. Lastly, the ACE decompositions of the covariance terms was used to estimate the degree of genetic and environmental correlation between the growth parameters of each phenotype, such as whether parental monitoring and substance use share genetic or environmental influences.

To assess whether the sample was sufficiently well powered to identify random effects correlations, ACE, parameters, and biometric correlations, a number of post-hoc power analyses were conducted. Power analyses for correlations between growth parameters were conducted via simulation. Using the "mvrnorm" function from the MASS package in R (40), data were simulated for each of the 10 combinations of phenotypes in samples of 670 participants measured at 24 timepoints, representing a full two-year participation period in the study. Data were simulated as arising from a bivariate growth model with random intercept, slope, and quadratic effects that were allowed to correlate across phenotypes. Random effects terms were generated with means of 0 and variances taken from the results of the original ACE-decomposed latent growth-curve models (presented in Supplementary Table S1). To account for missing data, 50% of observations were set as missing. Bivariate growth models analogous to those from the primary analysis, but without ACE components, were then fit to each simulated dataset. Simulations were repeated 100 times while varying correlations between random intercept, slope, and quadratic parameters to determine the minimum value of each random effects correlation that could be detected 80% of the time at an alpha level of 0.05. Eighty percent power to detect phenotypic correlations was achieved for 13/30 parameters at $r = 0.15$, for 20/30 parameters at $r = 0.25$, and for 25/30 parameters at $r = 0.35$. Lastly, power analyses for standardized multivariate ACE components were conducted via simulation using the "powerFun" functions described in Verhulst (41). Eighty percent power to detect genetic variance components was achieved at $A = 0.40$ when $C = 0$ and at $A = 0.34$ when $C = 0.2$. Similarly, 80% power was achieved to

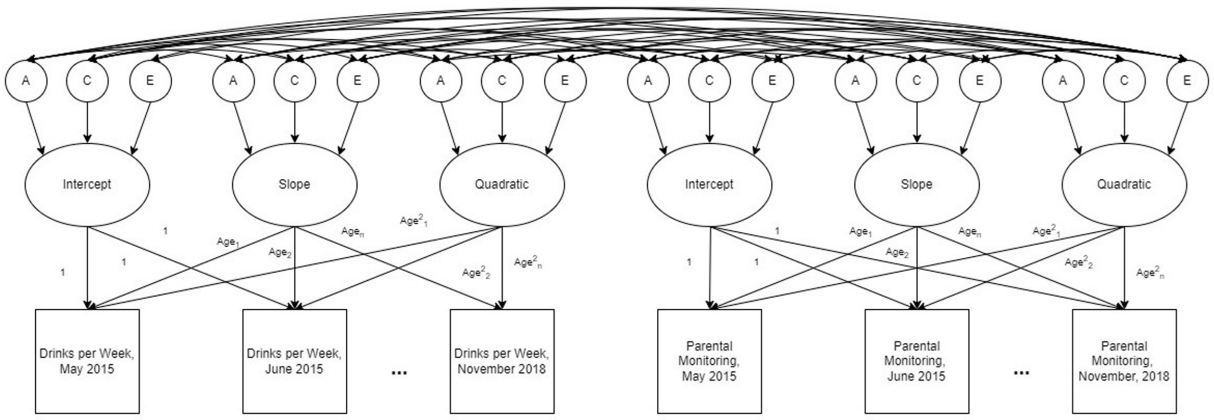

FIGURE 1
An example path diagram representing the ACE decomposed multivariate latent growth model for drinks per week and parental monitoring. The model estimates random effects, including intercepts, age slopes, and age quadratic terms, for each participant as well as the additive genetic (A), shared environmental (C), and non-shared environmental (E) contributions to these random effects. Genetic correlations (r_g), shared environmental correlations (r_c), and nonshared environmental correlations (r_e) between random effects terms are represented by the paths between the A, C, and E terms. Additional bivariate models were run comparing drinks per week, cannabis use per week, perceived parental monitoring, time spent at school, and time spent at home.

detect C variance components of C = 0.22 or greater with moderate genetic effects, A = 0.50 and at C = 0.25 when genetic effects were assumed to be small (e.g., A = 0.30). Assuming modest shared environmental influences of C = 0.20, models achieved 80% power to detect genetic correlations, the degree to which genetic influences are shared between two traits, when $r_g = 0.26$ between highly heritable traits (A = 0.70) and when $r_g = 0.72$ for moderately heritable traits (A = 0.5). Genetic correlations between more modestly heritable traits (A = 0.30) could not be reliably detected, achieving only 18% power even when $r_g = 1.00$.

3. Results

3.1. Mean phenotypic trajectories

During the remote assessment period, the rate of survey completion was consistent during the first year, with some decline during the second (Supplementary Figure S1A). The most frequently used substances in these assessments were alcohol (use reported in 6.9% of measurement occasions) and cannabis (use reported in 5.0% of measurement occasions).

Average developmental trajectories in substance use, parental monitoring, and the geospatial variables, measured via GAMMs, are presented in Figure 2. Both alcohol and cannabis use (Figure 2A) increased with age, with rapid acceleration after age 18, even on the log scale. The mean trajectory of parental monitoring (Figure 2B) demonstrated the expected decrease of parental monitoring with age; the decrease accelerated after age 18. Time at home and school estimated from GPS recordings (Figure 2C), both decreased with age, with rapid decreases between age 18 and 19 and relatively little change after age 19. Overall, these mean trajectory plots show average developmental increases in substance use and decreases in parental monitoring and geospatial measures as participants aged, with clear inflection points in all phenotypes around age 18.

3.2. Parental monitoring and substance use trajectories

The phenotypic correlations between participants' growth parameters in the latent growth models (intercepts, age slopes, and age quadratic terms) are reported in Table 2 while their covariances are presented as a supplement in Supplementary Table S1. Moderate to large positive associations were identified between substance use growth parameters: the random intercepts ($r = 0.65$), slopes ($r = 0.30$), and quadratic terms ($r = 0.55$) of weekly alcohol and cannabis use were all significantly correlated, indicating that developmental trajectories in these substances are positively related to one another during adolescence.

Our hypothesis that parental monitoring and substance use would be negatively correlated before age 18 was supported at baseline: we found a significant negative correlation of the random intercepts for parental monitoring and both alcohol and cannabis use ($r = -0.29$ to -0.24). However, changes in parental monitoring from ages 14 to 18 were not significantly associated with changes in substance use at this time: no significant correlations were identified between the slopes or quadratic terms for parental monitoring and alcohol or cannabis use ($r = -0.14$ to 0.10, all likelihood-based 95% confidence intervals included 0). Hence, while at age 14, participants who initially experienced higher parental monitoring were likely to experience lower initial levels of substance use, participants who experienced larger changes in parental monitoring during adolescence did not exhibit larger changes in either drinking or cannabis use.

3.3. Trajectories of geospatial measures

Turning next to results related to our geospatial measures, after quality control, 7,866,643 unique locations were recorded from 588 twins with a median of 7,956 locations per twin. Location tracking was implemented in the smartphone apps months after recruitment began,

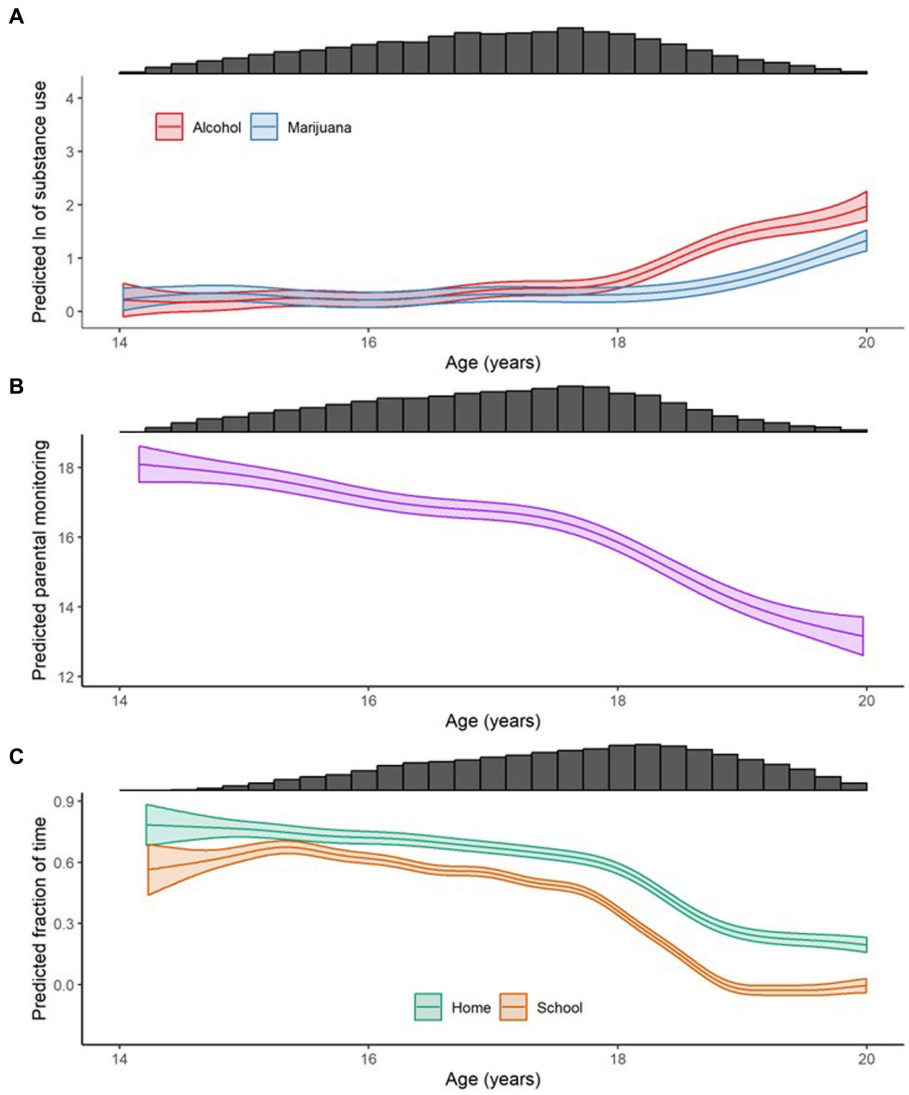

FIGURE 2
Smoothed means (on log scale) conditional on age, as calculated with generalized additive mixed models, of **(A)** natural log-transformed ("ln") drinks per week (Alcohol), cannabis uses per week (Cannabis), and e-cigarette uses per week (E-Cigarettes); **(B)** parental monitoring; and **(C)** the fraction of time spent at the family home at night (Home) and the fraction of time spent at school during the school day (School). Uncertainty in the estimate is shown as 95% confidence intervals and the marginal histograms show the relative number of data points available for a given phenotype in a given age range.

which is reflected in the number of locations recorded per twin over time (Supplementary Figure S1B). The rate of location acquisition was otherwise consistent over time, aside from a drop in the second year of remote assessment. One known difference between Android and iOS locations were that the Android location API was designed to record a location approximately every 5 min while the iOS application was designed to record a location only when the twin moved more than 500 m. These patterns are apparent in the distributions of the time and distance between successive points (see Supplementary Figure S2). Consecutive location points were very rarely further apart than 1 day or 100 km. Supplementary Figure S3 shows the distribution of forward filling for iOS locations, consistent with expectations that more forward filling would occur in the middle of the night and on weekdays. Fills that start between 8 PM and 3 AM, between 7 AM and 9 AM, or on Monday through Thursday are longer, reflecting twins' tendency to move less at night, on weekends, and during the school day.

Time at home and time at school before age 18 showed the expected patterns with time of day and day of week with time at home higher at night than during the day and lower on weekend nights than during the week (Figure 2 and Supplementary Figure S4). Time at school was highest on school days, during school hours and slightly lower on Friday than other school days. Time at school was also much lower on school holidays than other weekdays, supporting the validity of the assessment (Supplementary Figure S5).

The geospatial variables, time at home and time at school, were significantly positively correlated with one another at both the intercept ($r = 0.38$) and quadratic slope levels ($r = 0.60$) while correlations between their linear slopes ($r = 0.34$) were of comparable magnitude but fell just short of statistical significance (results

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TABLE 2 Phenotypic correlations between random intercepts, slopes, and quadratic terms (obtained from latent growth-curve models) with 95% maximum likelihood-based confidence intervals.

Intercept: Intercept correlations				
	Alcohol	Cannabis	Parental monitoring	Home
Alcohol	**1**			
Cannabis	**0.65 (0.58, 0.70)**	**1**		
Parents	**−0.29 (−0.37, −0.19)**	**−0.24 (−0.32, −0.14)**	**1**	
Home	−0.16 (−0.34, 0.02)	−0.06 (−0.26, 0.15)	0.04 (−0.10, 0.18)	**1**
School	−0.11 (−0.29, 0.07)	−0.12 (−0.30, 0.06)	0.00 (−0.14, 0.15)	**0.38 (0.20, 0.53)**
Slope: Slope correlations				
	Alcohol	Cannabis	Parents	Home
Alcohol	**1**			
Cannabis	**0.30 (0.18, 0.42)**	**1**		
Parents	−0.12 (−0.26, 0.02)	−0.14 (−0.29, 0.02)	**1**	
Home	−0.18 (−0.39, 0.03)	**−0.53 (−0.72, −0.25)**	0.21 (−0.04, 0.47)	**1**
School	0.11 (−0.12, 0.32)	0.07 (−0.31, 0.40)	−0.01 (−0.30, 0.29)	0.34 (−0.02, 0.67)
Quadratic: Quadratic correlations				
	Alcohol	Cannabis	Parents	Home
Alcohol	**1**			
Cannabis	**0.55 (0.40, 0.68)**	**1**		
Parents	0.10 (−0.10, 0.30)	−0.06 (−0.33, 0.23)	**1**	
Home	−0.26 (−0.58, 0.08)	**−0.90 (−0.96, −0.74)**	**0.47 (0.08, 0.74)**	**1**
School	0.15 (−0.20, 0.48)	0.44 (−0.36, 0.70)	−0.42 (−0.74, 0.03)	**0.60 (0.23, 0.82)**

Estimated cross-phenotype correlations and 95% confidence intervals between random intercepts, age slopes, and age quadratic effects in latent growth curve models. Included assessments were collected from ages 14 to 18. "Alcohol" and "Cannabis" are log transformed drinks per week and log transformed cannabis uses per week, "Parents" was the maximum parental monitoring score reported by any parental figure at a given timepoint, and "Home" and "School" represent the fraction of time spent at home between midnight and 5 am and the fraction of time spent at school between 8 am and 3 pm. Bolded values indicate correlations where 95% CIs did not include 0.

presented in Table 2). These findings indicate developmental trajectories from age 14 to 18 for both going out late at night and being away from school during school hours are positively correlated.

These geospatial variables were hypothesized to represent an alternative measure of the parental monitoring construct during adolescence, but both time at home and time at school were weakly and non-significantly correlated with parental monitoring at both the linear slope and intercept levels ($r = -0.01$ to 0.21, all likelihood-based 95% confidence intervals included 0). There was modest evidence for a relationship at the quadratic level, where parental monitoring was significantly correlated with time at home ($r = 0.47$) and nearly with time at school ($r = -0.42$), though this relationship with time at school was in the opposite of the expected direction and fell short of statistical significance.

While neither time at home nor time at school showed the expected relationships with parental monitoring from age 14–18, time at home (though not time at school) appeared related to substance use. Time at home was not significantly correlated with either alcohol or cannabis use at baseline, though its intercept-level correlation with alcohol use ($r = -0.16$) fell just short of statistical significance. Linear and quadratic changes in time at home showed small to moderate correlations with changes in alcohol use that were not statistically significant ($r = -0.26$ to -0.18) as well as large, statistically significant associations with changes in cannabis use ($r = -0.53$ to -0.90).

3.4. Twin-based biometric decomposition analyses

Biometric ACE decompositions of the random effects, which estimate the contributions of genetic, shared environmental, and nonshared environmental influences to the growth parameters for each phenotype, are reported in Figure 3. Biometric correlations, which tested the extent to which genetic and environmental influences are shared across phenotypes, are presented in Table 3 (unstandardized biometric covariance terms are included as Supplementary Table S1). Due to power constraints, many biometric correlations were estimated with wide confidence bounds, which limited the number of significant effects detected in these models.

Consistent with expectations, baseline alcohol and marijuana use and their developmental trajectories were all significantly heritable (A = 0.10–0.54). Shared environmental factors only significantly contributed to baseline alcohol use (C = 0.33). Similarly, initial levels and developmental changes in parental monitoring were significantly heritable (A = 0.30–0.67), indicating that an adolescent's reported level of parental monitoring is in part influenced by their genes. Shared environmental influences contributed modestly to baseline parental monitoring (C = 0.22) while non-shared environmental influences made moderate contributions to all three parental monitoring growth parameters (E = 0.26–0.47).

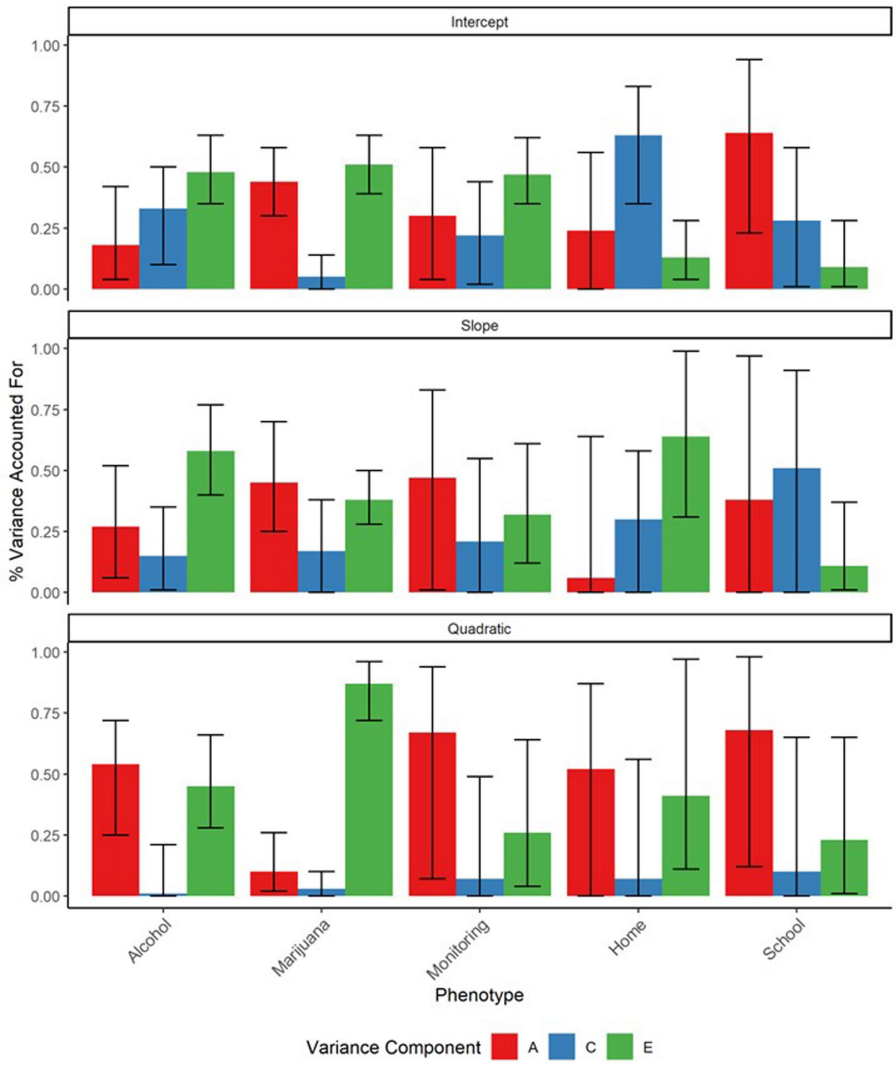

FIGURE 3
ACE decompositions of the random effects terms for drinks per week, cannabis use per week, parental monitoring, time spent at school, and time spent at home. Substance use phenotypes were aggregated monthly. "A" represents the proportion of variance in the trait attributable to additive genetic effects, "C" represents the proportion attributable to shared environmental effects, and "E" represents the proportion attributable to non-shared environmental effects. Error bars represent 95% maximum likelihood-based confidence intervals.

We did not find support for our hypothesis that relationships between parental monitoring and substance use would in part reflect gene–environment correlation. We found no significant genetic correlations for either of the significant, intercept-level relationships between parental monitoring and substance use, or for any of the other (nonsignificant) parental monitoring-substance use relationships. Hence, while we found that both parental monitoring and substance use were significantly influenced by genetic effects, we did not find evidence that genetic correlation significantly contributed to relationships between them. Instead, the significant relationship between baseline alcohol use and parental monitoring was found to be largely explained by the shared environment ($r_c = -0.61$), which accounted for 68% of the covariance between alcohol and parental monitoring intercepts. Hence, we found evidence that the baseline relationship between parental monitoring and alcohol use largely reflected mutual shared environmental influences. However, due in part to power constraints, none of the biometric correlations between baseline cannabis use and parental monitoring were significant.

Lastly, biometric analyses also revealed that the significant slope-level relationship between time spent at home and cannabis use was accounted for by mutual genetic ($r_g = -1.00$) and nonshared environmental ($r_e = -0.41$) influences, with genetic factors accounting for 9% and nonshared environmental factors for 88% of their relationship. At the quadratic level, only this nonshared-environmental component remained significant ($r_e = -0.92$), accounting for 93% of the relationship between the cannabis and time at home quadratic terms. These results suggest that adolescents who went out at night more as they grew older also increased their cannabis use and that this relationship in part reflects mutual genetic and non-shared environmental influences on these processes. These participants may also have, to a lesser extent, increased their alcohol use, though these relationships were non-significant in these models. We did not

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TABLE 3 Biometrically decomposed cross-phenotypic correlations between random intercepts, slopes, and quadratic terms (obtained from latent growth-curve models) with 95% maximum likelihood-based confidence intervals.

Intercept: Intercept correlations				
	Alcohol	Cannabis	Parents	Home
Cannabis	**$r_g = 0.90$**			
	$r_c = 0.85$			
	$r_e = 0.59$			
Parents	$r_g = -0.26$	$r_g = -0.35$		
	$r_c = -0.61$	$r_c = -0.81$		
	$r_e = -0.12$	$r_e = -0.03$		
Home	$r_g = 0.25$	$r_g = -0.46$	$r_g = -0.22$	
	$r_c = -0.44$	$r_c = 0.25$	$r_c = 0.09$	
	$r_e = -0.07$	$r_e = 0.22$	$r_e = 0.35$	
School	$r_g = 0.40$	**$r_g = -0.35$**	$r_g = -0.48$	$r_g = -0.08$
	$r_c = -0.79$	$r_c = -0.61$	$r_c = 0.55$	$r_c = 0.78$
	$r_e = -0.02$	$r_e = 0.54$	**$r_e = 0.52$**	$r_e = 0.98$
Slope: Slope correlations				
	Alcohol	Cannabis	Parents	Home
Cannabis	$r_g = -0.32$			
	$r_c = 0.70$			
	$r_e = 0.67$			
Parents	$r_g = 0.07$	$r_g = 0.01$		
	$r_c = 0.18$	**$r_c = -0.62$**		
	$r_e = -0.43$	$r_e = -0.15$		
Home	$r_g = -0.55$	**$r_g = -1.00$**	$r_g = -0.35$	
	$r_c = 0.29$	$r_c = -0.14$	$r_c = 0.42$	
	$r_e = -0.29$	**$r_e = -0.41$**	$r_e = 0.47$	
School	**$r_g = 0.74$**	$r_g = 0.52$	$r_g = -0.37$	$r_g = 0.69$
	$r_c = 0.14$	$r_c = -0.20$	$r_c = 0.35$	$r_c = 0.36$
	$r_e = -0.69$	$r_e = -0.66$	$r_e = 0.33$	$r_e = 0.15$
Quadratic: Quadratic correlations				
	Alcohol	Cannabis	Parents	Home
Cannabis	$r_g = 0.49$			
	$r_c = 0.90$			
	$r_e = 0.67$			
Parents	$r_g = 0.30$	$r_g = -0.17$		
	$r_c = -0.29$	$r_c = -0.06$		
	$r_e = -0.22$	$r_e = -0.09$		
Home	$r_g = -0.35$	$r_g = -0.89$	$r_g = 0.27$	
	$r_c = 0.15$	$r_c = -0.91$	$r_c = 0.04$	
	$r_e = -0.19$	**$r_e = -0.92$**	**$r_e = 0.29$**	
School	**$r_g = 0.73$**	$r_g = 0.77$	**$r_g = -0.72$**	$r_g = 0.66$
	$r_c = -0.85$	$r_c = 0.74$	$r_c = 0.40$	$r_c = 0.73$
	$r_e = -0.84$	$r_e = 0.81$	$r_e = -0.16$	$r_e = 0.79$

Cross-phenotype biometric correlations obtained from ACE decomposed latent growth curve models. Included assessments were collected from ages 14 to 18. Biometric correlations represent the degree to which genetic, shared environmental, and nonshared environmental influences are shared between phenotypes. "Alcohol" and "Cannabis" are log transformed drinks per week and log transformed cannabis uses per week, "Parents" was the maximum parental monitoring score reported by any parental figure at a given timepoint, and "Home" and "School" represent the fraction of time spent at home between midnight and 5 am and the fraction of time spent at school between 8 am and 3 pm. Bolded values indicate correlations where 95% confidence intervals did not include 0.

observe similar relationships between substance use and time at school.

4. Discussion

In this study, we investigated whether changes in adolescent-reported parental monitoring, a popular intervention target in parent management training interventions, are associated with corresponding changes in adolescent substance use and the extent to which genetic variation contributes to the observed relationship between parental monitoring and substance use. To do so, in a sample of 670 twins during mid-to-late-adolescence, we assessed fine-grained changes in substance use, parental monitoring, and two novel geospatial variables, time spent at home overnight and time spent at school during school hours, which were hypothesized to provide additional information on the parental monitoring construct.

Prior work has shown that substance use can be measured using ecological momentary assessment, such as weekly questions (42, 43), but previous studies of adolescent substance use development have typically had a frequency of assessment measured every few years or used a single occasion of measurement. In contrast, our approach provided much more frequent measurements of substance use over the course of 2 years. More frequent measurements allowed us to evaluate how constructs may change together over time, beyond evaluation of simple difference scores. This advantage is particularly important in studying adolescent substance use behavior due to the rapid changes in substance use behavior seen during this period and its importance to the development of substance use throughout the lifespan (44). Additionally, high frequency GPS-based location data are potentially powerful because it can be linked to other data sets with geographic information, such as maps with place information. These passively collected measures are less susceptible to reporting biases inherent to self-report and thus may be useful in augmenting self-report-based measures of constructs like parental monitoring.

In accord with previous studies, we found that adolescent substance use rates increase dramatically during high school, and additionally found decreases in average levels of parental monitoring, time at school, and time at home over the same period (44, 45). A notable property of all these behaviors is an inflection after age 18 (Figure 2), likely reflecting adolescent maturation and increases in autonomy.

Initial levels of substance use at age 14 (i.e., the random intercept) were correlated with initial level of parental monitoring, though changes in parental monitoring were not significantly related to changes in substance use from ages 14 to 18. The lack of significant correlations between changes in these behaviors fails to support the hypothesized causal effect of parental monitoring on adolescent substance use leveraged by many popular substance use interventions. Nonetheless, significant baseline-associations between these constructs at age 14 suggest there may be such a relationship in early adolescence. We thus cannot rule out that parental monitoring is an important protective factor in early adolescence, and thus may remain a valuable intervention target for delaying substance use, even if later changes in parental monitoring during mid-to-late adolescence are less effective.

Regarding whether genetic confounders influence the relationship between parental monitoring and substance use, we found that substance use and parental monitoring phenotypes were heritable traits. Parental monitoring, though conceived of as an aspect of the adolescent's environment, was generally found to be even more heritable than substance use was. This is consistent with previous studies on the heritability of parental monitoring, which, at least outside of disadvantaged environments, have found considerable genetic contributions to parental monitoring behaviors in childhood and adolescence (46, 47). This finding may reflect the effect of other heritable behavioral traits, like adolescent personality or parental closeness, on the level of parental monitoring that they experience. The finding that parental monitoring is heritable does not mean the trait is immutable, or particularly resistant to intervention, though the heritability statistic is occasionally misinterpreted in this fashion (48). Indeed, many highly heritable traits are readily susceptible to interventions (eyeglasses for astigmatism, or mood stabilizing medications for bipolar disorder are two such examples); thus, the heritability of parental monitoring has little implication for whether parent management trainings may effectively improve parental monitoring.

Furthermore, though both substance use and parental monitoring were heritable, we did not detect significant genetic correlations between them. Thus, we did not find evidence that genetic confounding underlies the intercept-level relationship we observed between parental monitoring and substance use. Contrastingly, we did find a significant shared (r_c) environmental correlation underlying this relationship. One interpretation of this is that parental monitoring represents an environmental influence on baseline substance use. Alternatively, aspects of the shared environment, like sociodemographic characteristics, or school and neighborhood effects, may simultaneously influence both substance use and parental monitoring in early adolescence.

The geospatial measures showed the expected relationships with the day of the week, the hour of the day (Figure 4), and the Colorado public school calendar (Supplementary Figure S5), evidencing substantial measurement validity. Contrary to our hypothesis and despite the apparent validity of these geospatial measures, evidence for a relationship between parental monitoring and either time spent at home or at school was weak. This result suggests that adolescents who go out late at night more often or who are more likely to miss school during the day report similar levels of parental monitoring as their peers who engage in lower levels of these behaviors.

Given our hypothesis that these variables measure discordance between a twin's actual and expected location, this finding is counterintuitive. One explanation is that participants may be disclosing these incidents to their parents, in which case engaging in them more frequently would not impact parental monitoring. Alternatively, it is possible that this time at home variable may also be capturing events unrelated to parental monitoring. These may include overnight stays with friends or relatives or, particularly for the children of divorced parents, at alternative home addresses not provided to the study. Similarly, adolescents may spend less time at school during school hours for many reasons, such as illness or homeschooling that are also unrelated to parental monitoring. Regardless, the lack of associations observed between parental monitoring and these geospatial variables suggest that they are likely not appropriate measures of the parental monitoring construct, at least when it is adolescent reported. To better understand the behavioral constructs that underlie these geospatial measures, additional research on their behavioral correlates is needed.

Time spent at home, though not initially correlated with substance use, showed a strong, negative correlation with changes in cannabis use

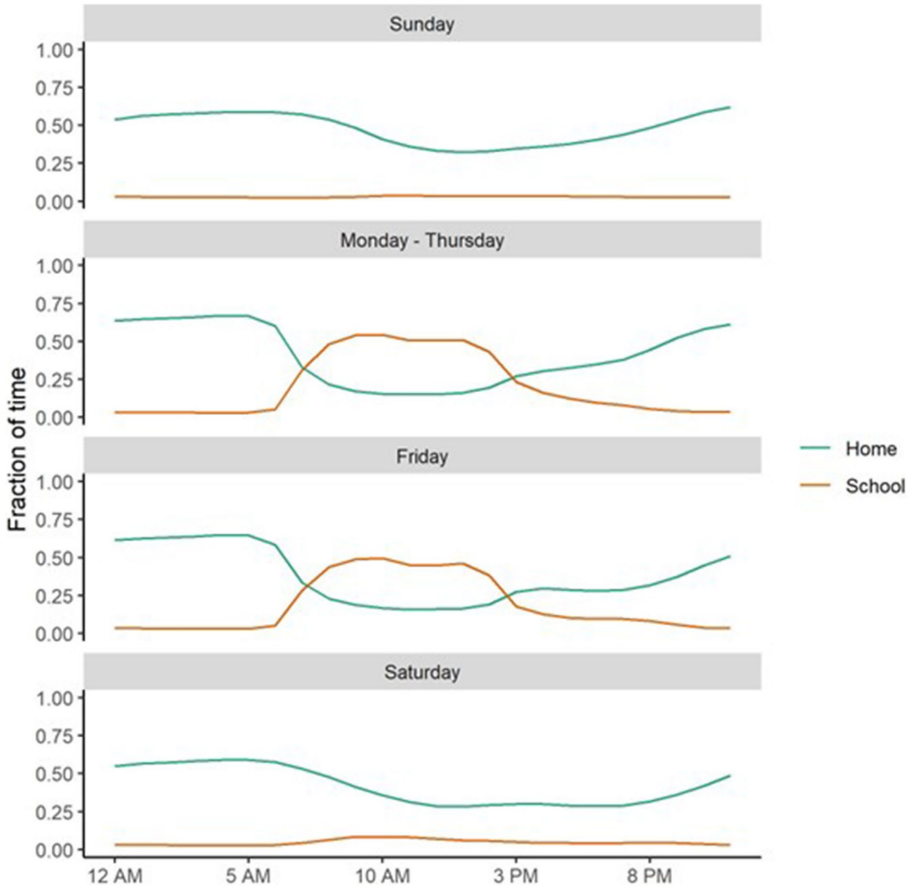

FIGURE 4
The fraction of time spent at home at night (Home) and at school, during school hours, on school days (School), conditional on time of day and day of week.

that was explained by mutual genetic and nonshared environmental influences. This included a perfect −1.00 genetic correlation between the slopes of cannabis and time spent at home, suggesting a strong overlap between the genetic influences on increasing substance use and increased time spent out at night. Thus, the processes influencing whether adolescents go out late at night more as they grow older, which may reflect behaviors like sneaking out late at night to attend parties or see friends, may be strongly influenced by genetic factors associated with risk taking behaviors like substance use.

Due in part to the novel data collection effort, several limitations are noteworthy. First, we required that study participants have a smartphone. While smartphone ownership is true for most youths aged 14–17, it is not universal. This inclusion criterion no doubt contributed to the ethnic and socioeconomic characteristics of the sample. Second, several factors may have contributed to measurement error or bias in the computation of our geospatial variables. While the location API provided estimates of point accuracy, these were not externally verifiable and so include some degree of measurement error. The large size of many suburban and rural high schools in Colorado may have resulted in some miss-classification of GPS points. Additionally, our measure of time at home at night is likely to be downwardly biased in families where a child sometimes stays with relatives or in families where the parents do not live together, as our set of home addresses for a family may not include all homes for those twins. Hence, measures of time at home and time at school may in part reflect behaviors, like attending a large high school or frequently visiting relatives that are less relevant to the parental monitoring construct. This may in part explain their low correspondence with adolescent-reported parental monitoring. Third and relatedly, parental monitoring was adolescent reported rather than parent-reported in this study. While parent and child-reported parental monitoring were positively correlated, they were only moderately so. It is thus possible that adolescent perceptions of parental monitoring may not be fully capturing the true extent of their parents' knowledge of their activities. Fourth, remote parental monitoring was measured via a subset of the parental monitoring items regarding perceived parental knowledge of their child's activities. Highly influential research on the parental monitoring construct has previously highlighted that parental monitoring is influenced by two additional constructs: parental solicitation and child disclosure, which were not assessed at the remote follow up assessments (15). Because of this, we are unable to say whether our baseline relationships between substance use and parental monitoring are driven more by parental solicitation efforts or by adolescent self-disclosure to their parents.

Fifth, this study assesses real-world developmental changes in parental monitoring and substance use in a community sample.

Though we failed to find corresponding changes in substance use and parental monitoring, the processes driving such changes in our sample may differ in important ways from those involved in parental management training programs, where changes in parental monitoring are induced via intervention and which are carried out in populations with clinically significant substance use or other behavioral difficulties. It is hence possible that their relationship may differ in heavier users or when parental monitoring is undergoing intervention, though additional theory would need to be developed and tested to understand why this would occur. Lastly, this study was conducted in a sample of 670 twins, which was underpowered to detect smaller genetic or environmental correlations, especially when the relevant variance components were small (41). This likely contributed to the wide confidence bounds around ACE estimates and the small number of significant biometric correlations. Hence it is possible that additional genetic and environmental correlations relevant to these relationships were not observed here due to power constraints.

With these limitations in mind, the present study has significant implications for our understanding of the relationship between parental monitoring and substance use. Namely that, at least in community samples, changes in parental monitoring are largely uncorrelated with changes in substance use in mid-to-late adolescence. This suggests that researchers should further explore whether parental monitoring is truly an effective intervention target in substance use interventions in this age group. While meta-analytic work supports the efficacy of parent-management training programs for substance use, additional work may be needed to understand the active ingredients driving these treatments. Further testing the theory underlying these treatments and conducting dismantling studies aimed at isolating their mechanisms of action will help enhance our understanding of these popular interventions and allow for more efficacious, cost-effective treatments in the future.

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 University of Minnesota and University of Colorado institutional review boards. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JA: conceptualization, data management, methodology, analytic strategy, statistical programming and analyses, wrote manuscript draft, and visualization of results. SF: statistical consulting, data management, and reviewed and edited the manuscript. SZ: statistical consulting, statistical programming, and reviewed and edited the manuscript. RC: grant oversight, initial data collection, project administration, data management, and reviewed and edited the manuscript. AL: data collection, data management, project administration, and reviewed and edited the manuscript. RS: data collection, project administration, and reviewed and edited the manuscript. CP and HS: data management and reviewed and edited the manuscript. MF and SR: data collection, data management, and reviewed and edited the manuscript. GR-S, MS, and HV: data collection and reviewed and edited the manuscript. MJ and QZ: grant oversight and reviewed and edited the manuscript. YL, ML, MM, SW, and PR: reviewed and edited the manuscript. JH: grant oversight, data management, and reviewed and edited the manuscript. NF: grant oversight, project conceptualization, supervision, statistical consulting, and reviewed and edited the manuscript. SV: grant oversight, project conceptualization, primary supervision, statistical consulting, and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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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.2023.1149079/full#supplementary-material

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Pilot data findings from the Gothenburg treatment for gaming disorder: a cognitive behavioral treatment manual

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Background: Gaming disorder (GD) is a new diagnosis included in the latest edition of the International Classification of Disease –11. Recently conducted international studies suggest a prevalence rate close to 2% for GD, highlighting the need for effective treatments for this patient population. Internationally there are few studies investigating effective treatments specifically designed for this condition. In this pilot study, we wanted to test a newly developed method, the Gothenburg Treatment for Gaming Disorder (GOT-TO-GO) manual; a 15-week cognitive behavioral therapy treatment for GD.

Method: This study utilized a single group design with pretest, post-test and a three- and six-month follow-up, with measures of severity of GD and mood. The participants (n=28) were treatment-seeking adults with GD, aged 17 to 49 years.

Results: The results show a statistically significant decrease in symptoms of GD after treatment. Hours of gaming per week also decreased concomitantly with a 100% increase in non-gaming leisure hours. The decrease in symptoms of GD was maintained at the 3-months follow-up after treatment. Correspondingly we saw a decrease in both depression and anxiety that also was upheld 3 months after treatment.

Conclusion: As GD is a new diagnostic concept more research is needed, also taking psychiatric comorbidity into consideration, to arrive at evidence-based conclusions regarding effective treatments. Considering the promising results in this small pilot study with large behavioral changes and reduced symptoms of GD, upheld at least 3 months after treatment, a larger randomized controlled study is warranted.

Clinical Trial Registration: https://www.clinicaltrials.gov/ct2/show/study/NCT05328596?term=NCT05328596&draw=2&rank=1, identifier NCT05328596.

KEYWORDS

adolescents, young adults, adults, treatment, CBT, gaming disorder, pilot

Introduction

In 2019, gaming disorder (GD) was included as a new diagnosis in the International Classification of Diseases (ICD-11) under the section for addiction (1). Gaming disorder is manifested by impaired control over gaming, increasing priority given to gaming and continuation or escalation of gaming despite the occurrence of negative consequences. In the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a similar construct named Internet Gaming Disorder was included among "Conditions for further studies" (2). Proposed criteria for this diagnosis include preoccupation, withdrawal, tolerance, reduced control, giving up other activities, continuing despite problems, deception, gaming to escape negative moods and risking or having lost relationships or opportunities. The suggested threshold for diagnosis is to fulfil at least five of these nine criteria in a 12-month period. As a consequence of being a newly defined disorder data on prevalence are scarce and inconsistent. Average worldwide prevalence of GD has been estimated at 1.96% with considerable differences between countries (3). Higher prevalence rates have been reported in specific groups, for example professional gamers with a prevalence rate of almost 4% (4).

There is evidence that GD often is accompanied by psychiatric comorbidity. A recent systematic review reported correlations between GD and anxiety, depression, ADHD, social phobia/anxiety, and obsessive–compulsive symptoms, with especially strong associations in adult populations (5). Regarding symptoms of ADHD, it is especially symptoms of inattention that are associated with GD (6). There are further findings that GD is associated with poor psychosocial functioning and lower performance in the academic or working spheres (7–9). Reduced self-satisfaction outside of playing video games, feelings of loneliness (10–12), negative affectivity and disinhibition (13) is also common. Whether these psychopathologies and impairments are risk factors for GD or consequences thereof, is not known and needs to be further studied longitudinally.

Gaming disorder is more common among men (3, 7, 14, 15) and among youth and young adults (3, 16). Low levels of family cohesion have been identified as a risk factor for GD in young adults and there is also a higher probability in this group of being unmarried, unemployed, having high levels of depression and anxiety (16–18), and a higher risk for suicide attempts (18) compared to individuals without GD. Several studies have shown that it is common among those with GD to use gaming to escape from negative emotions (18–20).

Cognitive behavioral therapy has been suggested as the most effective treatment for GD but has mostly been tested in a young population (21). There is also a scarcity of peer reviewed clinical treatment studies that include follow-up data to conclude if treatment gains are upheld over time (22). Regarding treatments for adults there are few studies that have evaluated the efficacy of a manualized CBT program (23–28) although both Wölfling et al. (25, 26) and Young (27, 28) designed their treatments for the broader concept of internet addiction (IA) including, i.e., online pornography and generalized internet addiction and not specifically for GD.

In an early CBT study that included 128 adults, decreased symptoms of IA was found and sustained at the six-month follow-up (27, 28). No control group was included. Further, the Short-term treatment of internet and computer game addiction (STICA) was tested in 143 young adults and improvements in symptoms related to IA was found compared to waitlist controls (26). In a non-randomized study, a CBT-approach for GD was compared with supportive therapy in 205 adults and reduced symptoms of GD was seen with results favoring CBT (23). Moreover, a multimodal treatment with CBT elements was tested in 40 adults and the severity of GD was decreased (24). Other CBT based psychotherapy studies has been conducted with younger subjects (12–22 years old), with 9 to 56 participants in each study, also showing positive results post treatment (29–34). Only three studies had a follow up period of three or six months (29, 30, 32).

Globally, more treatment research on GD is needed. It is therefore important to develop treatment manuals designed for this group of patients and evaluate their effects. This pilot study aimed to evaluate the effects and feasibility of a recently developed CBT treatment manual designed specifically for the treatment of GD. We first hypothesize that a 15-week CBT treatment will reduce symptoms of GD in a clinical population of young adults and adults fulfilling criteria for GD. We also hypothesize that a reduction of GD symptoms will be accompanied by a reduced amount of hours spent gaming each week. Our secondary hypothesis is that there will be a concurrent decrease in symptoms of psychiatric comorbidity such as depression and anxiety. We also have a third explorative hypothesis that the participants will experience an increased quality of life and have fewer symptoms of procrastination after treatment.

Materials and methods

This is a single group pilot study with pretest, post-test and a three-month follow-up. The study included 28 participants and was conducted from February 2020 to March 2023 (from inclusion of first participant to the last three-month follow-up) in Gothenburg, Sweden, at the Clinic for Gambling Addiction and Screen Health (Mottagning för spelberoende och skärmhälsa), Department of Addiction and Dependency, Sahlgrenska University Hospital, Region Västra Götaland. The clinic is the largest of its kind in Sweden offering specialized care for patients with gambling and gaming disorder. Patients were referred to the clinic either via self-referral or by other healthcare facilities. The treatment lasted for 15 weeks. After 3 months the patients were followed up with questionnaires. A smaller amount of participants were also followed-up after 6 months.

Subject recruitment and screening

The participants were consecutively recruited from the treatment-seeking population at the clinic. The initial assessment was conducted either as a videoconference or on site and included an anamnestic interview, a semi-structured diagnostic interview regarding symptoms of GD, screening for other psychiatric disorders, assessment of health, lifestyle, and psychosocial resources. After this assessment, made by a psychologist, a social worker or a nurse, participants were offered to enter the treatment program. All participants signed a consent form.

To be included in the study participants needed to fulfil the diagnostic criteria for Internet Gaming Disorder according to DSM-5 ($\geq$ 5 criteria). Participants had to be able to read and write Swedish fluently and have turned 15 years old. Participants were excluded if they had somatic or psychiatric conditions that contraindicated treatment or severely hindered treatment participation e. g. ongoing psychotic, manic or hypomanic episode, severe depression (PHQ 20–27 p) or neurodevelopmental disorder (e.g., ADHD or autism)

with low functional status evident by for example being in need of help with many activities of daily living, were currently in another psychological treatment with similar content as the one offered in the study or had started, or had ended or adjusted a medication for a psychiatric condition during the last 3 weeks. The study was approved by the regional ethics committee of the University of Gothenburg and complied with the guidelines of the Declaration of Helsinki (Dnr: 2020-07144).

The CBT-treatment for gaming disorder

There exists no gold-standard treatment of behavioral addictions. The Gothenburg Treatment for Gaming Disorder (GOT-TO-GO) is designed to focus on gaming specific problems. The treatment has been developed at the clinic and consists of CBT-techniques such as stimulus control, cognitive restructuring and relapse prevention commonly known from other treatment programs for GD (24, 32), addictive behaviors (25, 26, 32, 35–38) and substance use disorders (39–41) including behavioral self-control training (42). In addition, elements from motivational interviewing (MI) (43) are used, especially in the initial stages of treatment to strengthen the motives for behavioral change, as this method has been shown to be effective in supporting other types of behavioral change (44, 45). Motivational interviewing does probably not have a significant effect as a standalone intervention (46). However, using MI-exercises such as "decisional balance" serves as a useful framework to chart both positive and negative aspects of gaming, thereby laying groundwork for the formulation of individualized treatment goals.

The manual tested in this study was delivered with one session per week comprising 15 weeks. Additional support regarding psychosocial resources or health and lifestyle factors were offered if such a need was identified. The added support consisted of a few optional sessions (described more in detail below), in addition to the CBT-treatment.

To closely follow the patients' progression during treatment, they answered self-report questionnaires (dependent measures, see below) throughout the study (at baseline, mid-treatment, end of treatment and at follow-up). Starting at the first session, and continuing throughout the treatment, patients were also encouraged to keep track of their gaming activity via a weekly gaming diary.

The GOT-TO-GO treatment is divided in three phases: Initial stages, new skills and relapse prevention (for an overview see Table 1). *Phase 1*: In the initial phase individual goals for the treatment are formulated. Motivational techniques are also used to strengthen the patient's commitment to change. Goals are formulated both regarding gaming activity (what amount and type of gaming activity the patient wants to retain at end of treatment) and other changes the patient wants to make during treatment (for example to increase weekly exercise or to increase social activities outside gaming). Self-monitoring of gaming is introduced. *Phase 2*: Sessions follow with a focus on learning new skills to control gaming activity and to initiate other activities. The patients learn to identify their individual triggers for gaming, and strategies for stimulus control are implemented (for example uninstalling programs, moving the computer to another room, or blocking internet access for parts of the day). Much attention is also devoted to the introduction of new activities (behavioral activation), chosen individually to match the interests and goals of each patient, to fill some of the time otherwise devoted to gaming. Techniques for handling difficult feelings and unhelpful thoughts related to gaming are also introduced and practiced, as well as time-management and problem-solving skills. *Phase 3*: At the final stages a plan is formulated to maintain the changes made during treatment and how to get back on track if a relapse occurs. A summary is made of the most helpful techniques learned during treatment, the patients identify situations where they expect it would be especially difficult to maintain their changes and formulate strategies to tackle this (both proactive to stay on track and reactive to get back on track if they relapse). *Follow up*: After treatment is completed, the patients are contacted by phone for a follow-up after three and six months. As part of the follow-up the patients also fill out self-report questionnaires. If needed, two booster sessions are offered to analyze problematic situations that have occurred and to revise the relapse prevention plan. *Optional modules*: In addition to the above-mentioned sessions, there are also optional modules. Based on the intake assessment an individual plan for optional modules is made. An individual patient can take part in none, some, or all of these. The optional modules consist of (a) 1–3 family sessions where family members and/or significant others meet with the patient and, with assistance from a social worker, make plans on how to work together to reach the patient's treatment goals. This has been added as familial conflicts about gaming and lack of consensus about treatment goals might hinder change (47), and conversely that higher levels of family cohesion seem to be a protective factor against GD (16), (b) 1–3 additional sessions for support regarding psychosocial resources, for example to establish contact with other societal support systems, (c) 1–3 additional sessions for support regarding health and lifestyle factors, for example to initiate physical exercise or to cut down on alcohol use, (d) 1 additional session for support on how to plan and conduct home-work assignments throughout treatment.

The GOT-TO-GO manual is based on general techniques from other CBT-treatments for substance use disorders and behavioral addictions. Therefore, several parts are similar to other CBT-treatments [for example the method developed by Wölfling et al. (26)]. However, our manual also differs in many ways from other treatments for behavioral addictions and specifically gaming disorder. One essential difference is that the manual, unlike many other approaches, is specifically developed for gaming disorder. More specific differences are that strategies to control and limit gaming is implemented without a period of total abstinence, the manual consists of fewer sessions [15 sessions in total compared with 23 sessions described by Wölfling et al. (26)], and in the gaming diary, time spent gaming is separated from other types of time spent online. The intervention has been developed with a population with considerable psychiatric co-morbidity in mind. Handouts for patients have been made as simple as possible and a flexible system with additional sessions to meet individual needs has been designed. We also include family sessions to help the family support the patient and offer support to activate a professional network around the patient.

Variables and measures

Primary outcome measures

Gaming addiction identification test

The GAIT was our main outcome measure. GAIT is the only screening tool for GD developed and validated in a Swedish population. It consists of 17 questions regarding gaming that cover

TABLE 1 Content of the CBT-treatment for gaming disorder together with measure points.

Phase	Theme	Interventions	Measures
First visit	Assessment	Diagnostic assessment of Internet Gaming Disorder according to DSM-5 Anamnestic information Assessment of other psychiatric conditions Assessment of psychosocial resources Assessment of health and lifestyle factors	Baseline
Phase 1: Initial stages (Session 1–2)	Introduction and goal setting	Motivational interviewing Goal setting Introduction of self-monitoring strategies	Weekly gaming calendar
Phase 2: New skills (Session 3–12)	Learning new skills to gain control over the gaming activity and to initiate alternate activities	Psychoeducation Identification of individual triggers for gaming Time-management Stimulus control Behavioral activation Using skills from gaming to reach treatment goals Strategies to identify and handle feelings Strategies to identify and handle unhelpful thoughts Problem solving	Weekly gaming calendar + Mid-treatment
Phase 3: Relapse prevention (Session 13–15)	Making plans to maintain changes	Evaluation of treatment Individual plan to maintain changes and to handle relapses	Weekly gaming calendar + End of treatment
Follow-up		Follow-up on how changes have been maintained If needed: 2 booster sessions to revise the relapse prevention plan	Follow-up after 3 and 6 months
Optional	Additional support	Family sessions (1–3 sessions with the patient and his/her family members to formulate a plan on how to work together to reach the patient's treatment goals). Additional session for support regarding psychosocial resources Additional session for support regarding health and lifestyle factors 1 session with support on how to work with home-work assignments	

all the DSM-5 diagnostic criteria for Internet gaming disorder. The questions concern all digital games including games on computer, mobiles or TV, both gaming with others and alone (48). Suggested cut-off for GD is at least five questions being endorsed as "completely agree." For this study a version of the questionnaire has been used that covers gaming during the past 30 days. The 30-day version was used due to our repeated measure design with the aim to detect a change in symptoms of gaming disorder over the course of the 15-week treatment, as well as during follow-up at intervals of only 3 months. GAIT has very good internal consistency (Cronbach's alpha = 0.95).

Gaming disorder – time line follow back

We used a timeline follow back measure as our second main outcome measure. This type of measure was originally developed to track alcohol-consumption (49) but has been adapted for this study to track behaviors relevant to GD. The GD-TLFB is a diary where frequency and duration of weekly gaming can be tracked as well as other time spent online and time spent on screen-free activities. The gaming diary serves as a valuable complement to the symptom measures. Although the aim of treatment is to alleviate the negative consequences of gaming (the symptoms) and not time spent gaming *per se*, still, decreasing time spent gaming is a necessary step to reach that goal. Aside from being used as an outcome measure, the gaming diary also serves as an important clinical tool for self-monitoring.

Secondary measures

The Patient Health Questionnaire (PHQ-9) consists of nine items screening for symptoms of depression during the last 2 weeks. PHQ-9 is developed according to the diagnostic criteria in DSM-4 and the total score can be used to assess severity of depressive symptoms. Based on the total score the level of severity is classified as none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19) or severe (20–27) depression. PHQ-9 has been shown to have high validity in detecting severity of depression (50).

The Generalized Anxiety Disorder Assessment (GAD-7) was developed as an instrument to measure severity of symptoms of anxiety. It is a seven-item questionnaire screening for symptoms during the last 2 weeks. The total score is 21, and the scores indicate minimal (0–4), mild (5–9), moderate (10–14) or severe (15–21) anxiety (51).

Exploratory measures

The Brunnsviken Brief Quality of life scale (BBQ) measures an individual's subjective quality of life. It is divided into six different life areas that are rated individually regarding perceived importance and satisfaction. The maximum score is 96 with higher scores indicating higher levels of quality of life, and scores below 52 being associated with clinical samples (52).

The Pure Procrastination Scale (PPS) identifies the occurrence and severity of procrastination. It consists of 12 items rated on a 1–5

point Likert scale with higher scores indicating higher levels of procrastination (53).

Subject demographics

We also collected demographic data about the participants including age, sex, educational level, living situation and current occupation. Levels of alcohol and drug use were measured with the AUDIT (54) and DUDIT (55).

The Alcohol Use Disorders Identification Test (AUDIT) is a screening tool for alcohol related problems and identifies individuals with harmful use of alcohol. It consists of 10 items divided into three areas: alcohol consumption, symptoms of dependence and negative consequences of alcohol consumption. The maximum score is 40, with a cut-off score of 6 for women and 8 for men indicating hazardous or harmful drinking (54).

Drug Use Disorders Identification Test (DUDIT) is a screening tool for problematic use of illicit drugs. Like AUDIT, it is a 10-item instrument with a maximum score of 40. The questions are categorized in three areas, drug use, dependence symptoms and negative consequences of drug use. DUDIT scores of 1 or more for women and 3 or more for men indicate problematic drug use (55).

Data analysis

All analyses were conducted in IMB SPSS 28.0.1.1. Out of the 28 participants 12 were treated individually and the rest in group format. In the analyses, irrespective of having received the treatment via group or individual sessions, data from all participants have been included. The primary outcome variables were symptoms of GD measured by the GAIT and the four measures included in the gaming diary. Secondary measures included the PHQ-9, the GAD-7, and the exploratory measures were the BBQ and the PPS. The gaming diary consisted of nine repeated measures from the start of treatment to the last session of treatment. The GAIT, as well as the PHQ-9 and GAD-7 were also given at repeated intervals, at baseline, mid-treatment, termination of treatment, and 3-months follow-up. The BBQ and PPS instead were repeated at baseline, termination, and 3-months follow-up. For the gaming diary a total of 41% of data points were missing, ranging between 7% to at most 50% at specific timepoints and measures. For the GAIT, PHQ-9, and GAD-7 a total of 33% of data were missing, ranging from 4% at baseline to 57% at the 3-month follow-up. For the BBQ a total of 26% of data was missing, ranging from 4% at baseline and 57% at three-month follow-up. For the PPS a total of 42% of data was missing, ranging from 29% at baseline and 61% at 3-month follow-up.

Mixed-effects models fitted with maximum likelihood estimation were used to estimate individual changes over time during treatment (gaming diary) and from baseline to follow-up (GAIT, PHQ-9, GAD-7, BBQ, and PPS). Mixed effects models were used as they handle missing data and correlation between repeated measurements better than a classical repeated measures ANOVA (56, 57). Further, as the mixed model uses all available data points it is possible to do an intention-to-treat analysis, including all participants in the analysis.

For the primary outcome measure GAIT, a basic model with a fixed slope for *time* was created. *Time* was coded as 0–3 with 0 being baseline and 3 being 3-month follow-up. To account for possible non-linear effects a quadratic effect of *time x time* was tested, found non-significant and was therefore discarded. A random intercept and random slope for *time* was tested but did not improve the model according to a likelihood ratio test and were thus discarded. A heterogeneous first-order autoregressive covariance pattern was used for the repeated measures and was significant, $p < 0.001$.

Model building was approached in the same way for the secondary outcome PHQ-9, and *time* was similarly coded here. The quadratic effect of *time x time* was non-significant and discarded. A random intercept and random slope for *time* improved model fit according to a likelihood ratio test $p < 0.05$ and were retained. A diagonal covariance pattern was used for the repeated measures as the model did not otherwise converge. Unstructured covariance type was used for the random effects.

For the GAD-7 *time* was similarly coded. The quadratic term of *time x time* was non-significant and discarded. The random intercept and random slope for *time* did not improve model fit according to a likelihood ratio test and were discarded. A heterogeneous first-order autoregressive covariance pattern was used for the repeated measures and was significant, $p < 0.001$.

For the BBQ *time* was coded 0–2, with 0 being baseline, and 2 being three-month follow-up. The quadratic term of *time x time* was non-significant and discarded. When the random intercept and random slope for *time* was added the model failed to converge, and the model with random intercept were not an improvement according to a likelihood ratio test. The random effects were thus discarded. A heterogeneous first-order autoregressive covariance pattern was used for the repeated measures and was significant, $p < 0.001$.

For the PPS *time* was similarly coded. The quadratic term of *time x time* was non-significant and discarded. When the random intercept and random slope for time was added the model failed to converge. A model with diagonal covariance pattern and random intercept did converge and was a better model according to a likelihood ratio test. However, a model without random effects using a heterogeneous first-order autoregressive covariance pattern ($p < 0.001$) proved to have similar fit and was chosen as it was a simpler model.

As the 6 months follow-up was not conducted for all participants ($n = 9$ out of 28, $n = 8$ for the GAD-7) this timepoint was not included in the above models. The means and standard deviations for these participants are however presented for descriptive purposes.

For the primary outcome hours gaming/week a basic model with a fixed slope for *time* was created. *Time* was coded as 0–8 with 0 being diary entry pre-treatment and 8 the final entry during treatment. A quadratic fixed effect of *time x time* was tested to account for possible non-linearity. This effect was significant, $p < 0.05$ and was retained. A random intercept improved model fit according to a likelihood ratio test, $p < 0.001$ and was retained. A heterogeneous first-order autoregressive covariance pattern was used for the repeated effects and was significant, $p < 0.001$.

For days gaming/week model building was approached in the same way and *time* was coded similarly. The quadratic effect of *time x time* was non-significant and was discarded. A random intercept and random slope for *time* significantly improved model fit (likelihood ratio test, $p < 0.001$) and were retained. A diagonal covariance pattern was used for the repeated measures as the model did not otherwise converge. Unstructured covariance type was used for the random effects.

For non-gaming screen time, *time* was coded similarly. The quadratic effect was non-significant and discarded. A random intercept and random slope for *time* produced a model with better fit (likelihood ratio test, $p < 0.001$) and these effects were retained. A

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diagonal covariance pattern was used for the repeated measures as the model did not otherwise converge. Unstructured covariance type was used for the random effects.

For non-screen leisure time, *time* was coded in the same way. The quadratic effect was non-significant and discarded. A random intercept and random slope for *time* significantly improved model fit (likelihood ratio test, $p < 0.001$) and these effects were retained. A heterogeneous first-order autoregressive covariance pattern was used for the repeated effects and was significant, $p < 0.05$. Unstructured covariance type was used for the random effects.

Estimated means of variables were calculated for all time points in the mixed-models that yielded significant effects. Estimated means of non-significant models are not reported.

Cohen's d effect sizes were calculated for significant effects (58). For the mixed-models, Cohen's d was calculated between baseline mean and mean at the final time-point in the series using the model estimated means together with the observed standard deviation at baseline (59). Confidence intervals of within group effect sizes were calculated using Pearson correlations of observed values between baseline and the final time-point.

In the participants section, harmful alcohol use and problematic drug use was based on cut-off values for AUDIT (≥ 8 for men, ≥ 6 for women) and DUDIT (≥ 3 for men, ≥ 1 for women) scores (54, 55).

Results

Subject demographics

There were 28 participants included in this study, with an average age of 27.7 (SD 7.3) years. Of these, there was only one woman (3.6%), and the rest were men. The most preferred games were Massively multiplayer online role-playing games (MMORPG), Multiplayer online battle arena (MOBA) and First-person shooter games (FPS). In the sample, 71.5% had a high school education or higher. The majority 60.8% were employed or studying, 17.9% were on sick leave, 14.3% were unemployed and 7.2% had another occupation or some combination of the above. The most common living situation was living together with relatives/parents/friends (44.4%), followed by living alone (22.2%). Of the participants, 26.9% used nicotine in some form. Regarding alcohol and illicit drugs, 11.1% of participants had a harmful alcohol use based on AUDIT scores, and 11.1% a problematic drug use based on DUDIT scores. See Table 2 for a full list of subject demographics.

Of the 28 participants, 24 completed the 15 week GOT-TO-GO treatment resulting in a dropout rate at 14% which is below the normal rates (19–51%) in psychiatric health care (60).

TABLE 2 Subject demographics.

Demographic variables	Total sample (n=28)[a]
Age M (SD)	27.7 (7.3)
Age range	17–49
Gender %	
Men	96.4
Women	3.6
Preferred game genres (n)[b]	
MMORPG	10
MOBA	7
FPS	10
Other	9
Education %	
Less than high school	28.6
High school	28.6
Occupational training	17.9
University	25.0
Occupational status %	
Working	42.9
Sick-leave	17.9
Unemployed	14.3
Studying	17.9
Other/combination of above	7.2
Living Situation %	
Alone	22.2
With partner	18.5
With relatives/friends	44.4
Single parent	3.7
With partner and children	11.1
Nicotine use %	
Yes	26.9
No	73.1
Harmful alcohol use %[c]	
Yes	11.1
No	88.9
Problematic drug use %[d]	
Yes	11.1
No	88.9
Psychiatric co-morbidities[e]	
F10-F19 Substance use disorders	6
F20-F29 Schizophrenia etc.	1
F30-39 Mood disorders	21
F40-48 Neurotic disorders	8
F50-F59 Eating disorders etc.	3
F60-F69 Personality disorders	2
F80-F89 Autism etc.	2
F90-F98 ADHD etc.	7

[a]Partial missing data for living situation (n=1), tobacco use (n=2), AUDIT (n=1) and DUDIT (n=10).
[b]One individual can have several preferred game genres.
[c]Based on AUDIT scores.
[d]Based on DUDIT scores.
[e]Diagnostic categories according to classification with ICD-10. One individual can have several diagnoses.

Primary outcomes

The model estimates for the primary outcome of GD symptoms measured by the GAIT can be found in Table 3 along with confidence intervals, p-value and effect size. The model intercept of 42.52 is the estimated baseline score for all participants. The significant effect of time ($p < 0.001$) of −9.62 means that from each step between baseline to 3-month follow-up the GAIT score is reduced by X*9.62 points (baseline X = 0, mid X = 1, post X = 2, three-months X = 3). This means

TABLE 3 Model estimates of gaming behaviors, including confidence intervals, *p*-values and effect sizes.

Model	Estimate	95% CI	*p*-value
GAIT			
Intercept	42.52	39.64 to 45.39	< 0.001
Time (baseline to 3 months)	−9.62	−11.6 to −7.63	< 0.001
Within group effect size (Cohen's d)	4.03[a]	−0.97 to 9.4	
Hours/week			
Intercept	45.65	33.99 to 57.32	< 0.001
Time (pre-treatment to treatment final entry)	−8.33	−12.27 to −4.39	< 0.001
Time x Time	0.65	0.03 to 1.0	< 0.001
Within group effect size (Cohen's d)	0.63[b]	−0.99 to 2.08	
Days/week			
Intercept	5.57	4.65 to 6.49	< 0.001
Time (pre-treatment to treatment final entry)	−0.11	−0.28 to 0.05	= 0.164
Within group effect size (Cohen's d)	N/A		
Non-gaming screen hours/week			
Intercept	25.87	20.58 to 31.16	< 0.001
Time (pre-treatment to treatment final entry)	−0.73	−1.33 to −0.14	< 0.05
Within group effect size (Cohen's d)	0.36[b]	−1.91 to 2.49	
Non-gaming leisure hours/week			
Intercept	16.60	10.09 to 23.1	< 0.001
Time (pre-treatment to treatment final entry)	1.41	0.63 to 2.19	= 0.001
Within group effect size (Cohen's d)	0.75[b]	−0.18 to 1.97	

[a]Effect size is calculated between baseline and 3-month follow-up for GAIT.
[b]Effect size is calculated between baseline and the final week of treatment for the gaming diary.

that symptoms of GD decreased over time. This is illustrated in Figure 1, where model estimated means are plotted over time and compared to observed means with standard deviations. The observed mean for the limited number of 6-months follow-ups is also presented in Figure 1 for descriptive purposes. The effect size of change between baseline to 3-month follow-up was large, $d = 4.03$.

In Table 3 the model estimates together with *p*-values, confidence intervals and effect sizes for the various measures of gaming behavior derived from the gaming diary are reported. Participants were gaming at a model estimated average of 45.65 h/week at baseline. A significant effect of time (pre-treatment to final measurement) ($p < 0.001$) of −9.62 and time x time ($p < 0.001$) of 0.65 meant that hours/week were reduced during treatment, but the rate of change slowed down each week and even increased somewhat at the end of treatment (each step from baseline the score is reduced by $X*8.33 - X^2*0.65$). The model estimated hours/week at the final measurement was an average of 20.61 h/week. The effect size of the reduction from pre-treatment to the final measurement was medium sized, d = 0.63. There was also a significant effect of time ($p < 0.05$) of −0.73 regarding non-gaming screen hours/week. This means they were reduced linearly from a model estimated average of 25.87 h pre-treatment to 20.0 h at the final measurement. The effect size was small, d = 0.36. Non-gaming leisure hours instead significantly increased linearly over time ($p < 0.001$) with 1.41 for each measurement point during treatment. The model estimated an average of 16.6 h non-gaming leisure time at baseline, and 27.89 h at the final measurement. This was a medium sized effect, d = 0.75.

No significant change over time ($p = 0.164$) was found regarding the number of days/week participants were gaming. See Table 4 for observed means and standard deviations, and model estimated means for the measures in the gaming diary.

Secondary and exploratory outcomes

Symptoms of depression were found to significantly ($p = 0.001$) decrease linearly over time, from baseline to 3-month follow-up with a rate of −2.44 points on the PHQ-9 for each timepoint (baseline, mid-treatment, post-treatment, 3-months). The model estimated mean at baseline was 10.64 and this was reduced to a model estimated mean at 3-month follow-up of 3.33. The effect size of change was large, d = 0.98. Anxiety symptoms measured by the GAD-7 also decreased linearly over time ($p < 0.001$) with an estimated rate of −1.42 from an estimated baseline score of 7.21 to 3.09 at 3-month follow-up. This was a large effect, d = 0.80.

Procrastination, measured by the PPS, also decreased significantly over time ($p < 0.001$) by −5.58 for each timepoint (baseline, post-treatment, 3-months) from a model estimated 42.25 at baseline to 31.1 at 3-month follow-up, which was a large effect, d = 0.99. There was no significant effect of time on quality of life measured by the BBQ from baseline to 3-month follow-up, $p = 0.060$.

Model estimates, *p*-values, confidence intervals and effect sizes for the PHQ-9, GAD-7, BBQ, and PPS models can be found in Table 5. Observed means and standard deviations as well as model estimated

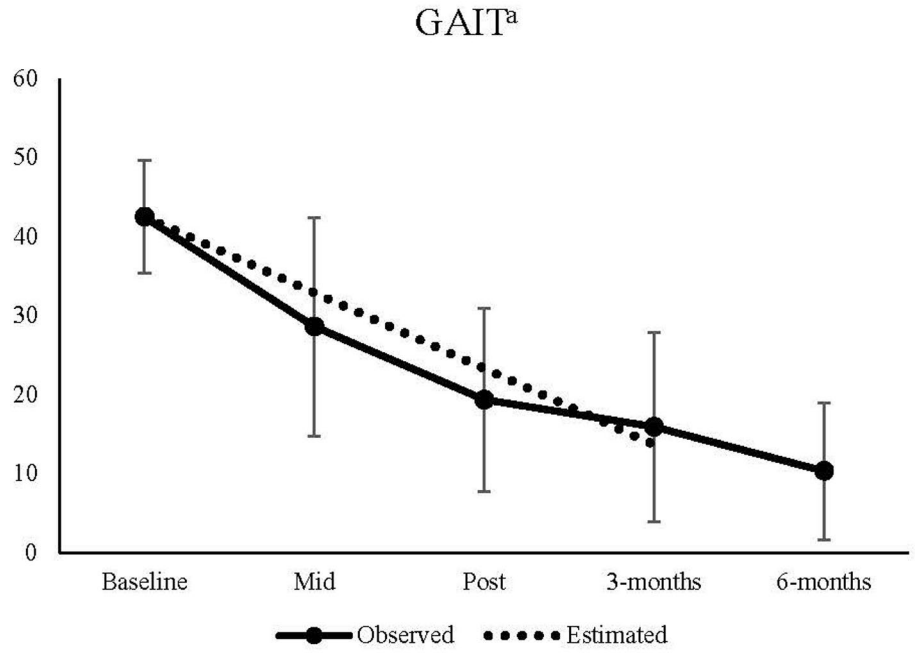

FIGURE 1
Observed means from baseline to 6-month follow-up, and estimated means from baseline to 3-months follow-up for the GAIT. [a]A significant effect of time, $p<0.001$ was found in the model.

TABLE 4 Time line follow back gaming diary.

Measure	Pre	Entry 1	Entry 2	Entry 3	Entry 4	Entry 5	Entry 6	Entry 7	Entry 8
Hours/week[b]									
Observed M[a]	51.71	40.08	29.62	24.79	22.82	16.9	18.81	16.93	19.5
Observed SD[a]	39.64	26.24	22.47	22.12	18.25	13.39	14.94	16.08	15.64
Estimated M	45.65	37.97	31.59	26.51	22.73	20.25	19.07	19.19	20.61
Days/week									
Observed M[a]	5.71	6.08	5.46	5.12	4.59	4.84	4.56	4.4	4.86
Observed SD[a]	2.34	2.02	2.35	2.33	2.56	2.43	2.39	2.67	2.66
Estimated M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Non-gaming screen hours/week[c]									
Observed M[a]	26.43	23.04	24.6	26.44	23.48	26.47	19.63	20.73	17.96
Observed SD[a]	16.37	14.63	11.73	11.15	13.2	16.93	11.21	8.87	7.95
Estimated M	25.87	25.13	24.4	23.67	22.93	22.2	21.46	20.73	20.0
Screen-free lesiure time									
Observed M[a]	12.89	17.81	21.81	26.91	26.45	31.89	30.63	31.7	34.36
Observed SD[a]	13.26	13.64	18.19	21.99	17.71	24.58	24.93	27.13	24.84
Estimated M	16.6	18.01	19.42	20.83	22.25	23.66	25.07	26.48	27.89

Means, standard deviations and model estimated means for all timepoints in the gaming diary.
[a]Based on all non-missing data. Missing data ranges from 7–50% at specific timepoints.
[b]A Significant effects of time, $p<0.001$ and time x time, $p<0.05$ were found in the model.
[c]A significant effect of time, $p<0.05$ was found in the model. [d]A significant effect of time, $p<0.001$ was found in the model.

means can be found in Table 6. Observed means for the limited number of 6-month follow-ups are for descriptive purposes also presented in Table 6.

Discussion

This was an uncontrolled pilot study intended to evaluate the feasibility of a newly developed manualized CBT treatment for patients diagnosed with GD. The 28 participants included in the study were followed from baseline to 3-months post treatment. We investigated symptoms of GD, sociodemographic factors, alcohol and drug use, depression and anxiety, quality of life and procrastination.

Sociodemographic characteristics

We notice both differences and similarities regarding sociodemographic characteristics when comparing the patients in our study with populations in earlier studies. The mean age in our sample was 28, meaning that we reached an older group than most previous clinical studies where the age range has been between 12 to 22 years of age (5, 29–34). However, both the age range and the high education level seen in our study is similar to other IA-studies with adult patients (26, 28).

In our study, only one woman chose to participate. The prevalence of GD is estimated to be 2.5 times higher among men than women, and therefore it is expected that more men than women will seek treatment. However, the proportion of women in our study and other treatment studies for GD (23, 24) are still much lower than could be expected based on prevalence. In this aspect, GD differs from other psychiatric conditions where women usually are overrepresented as treatment-seekers (61). Still, we believe it is important to continue including women in future treatment studies, and also make active efforts to reach more women with GD.

The association between GD and substance use has been investigated, but findings so far are mixed. We found that a small proportion of our patients had a problematic intake of alcohol or other drugs, to a comparable extent with the Wölfling et al. (26) study. Other studies have for example shown a positive correlation between severity of GD and frequency of substance use (63–65). Studies have also shown that those who play under the influence of for example stimulants, Ecstasy/MDMA, sedatives or amphetamines spend more time gaming than non-substance users (62) and that high alcohol consumption is an antecedent to gaming disorder (66). On the other hand, it has also been reported that a heavy investment in gaming may lead to a reduction in alcohol use (67) or that no association between alcohol and gaming disorder could be detected (63). Considering the findings that some treatment seekers with GD also have a problematic intake of alcohol or other drugs, together with the mixed research findings so far regarding associations between GD and substance use, we believe that it is important to regularly screen for possible co-morbidities with SUD in future treatment studies. Thereby, we can increase our knowledge on how substance use and SUD might affect treatment results, and if changes regarding gaming also are associated with changes in substance use.

Changes during treatment

We found a significant reduction in symptoms of GD between baseline measurements and the 3-months follow-up, in total a decrease by 70% based on measures with the GAIT. Similarly, hours spent gaming per week, measured with the GD-TLFB,

TABLE 5 Model estimates of non-gaming behaviors secondary outcomes, including confidence intervals, *p*-values and effect sizes.

Model	Estimate	95% CI	*p*-value
PHQ-9			
Intercept	10.64	8.0 to 13.29	< 0.001
Time (baseline to 3 months)	−2.44	−3.79 to −1.09	= 0.001
Within group effect size (Cohen's d)[a]	0.98	−1.23 to 2.97	
GAD-7			
Intercept	7.21	5.33 to 9.1	< 0.001
Time (baseline to 3 months)	−1.42	−2.2 to −0.63	< 0.001
Within group effect size (Cohen's d)[a]	0.80	−1.60 to 2.96	
BBQ			
Intercept	42.38	34.08 to 50.67	< 0.001
Time (baseline to 3 months)	5.33	−0.23 to 10.89	= 0.060
Within group effect size (Cohen's d)[a]	N/A		
PPS			
Intercept	42.25	37.02 to 47.49	< 0.001
Time (baseline to 3 months)	−5.58	−8.35 to −2.8	< 0.001
Within group effect size (Cohen's d)[a]	0.99	−0.49 to 2.44	

[a]Effect sizes are calculated between baseline and 3-month follow-up.

TABLE 6 Means, standard deviations, and model estimated means for non-gaming behavior secondary outcomes.

Measure	Baseline	Mid	Post	3 month	6 month[d]
PHQ-9[b]					
Observed M (SD)[a]	12.0 (7.44)	7.09 (5.45)	5.26 (4.57)	6.64 (8.03)	3.78 (3.38)
Estimated M	10.64	8.21	5.77	3.33	-
GAD-7[c]					
Observed M (SD)[a]	7.22 (5.31)	6.61 (4.6)	3.61 (3.37)	3.09 (2.74)	3.75 (5.9)
Estimated M	7.21	5.8	4.38	2.96	-
BBQ					
Observed M (SD)[a]	42.37 (21.37)	-	48.74 (18.7)	56.27 (16.73)	58.33 (23.89)
Estimated M	42.38	-	47.7	53.03	-
PPS[c]					
Observed M (SD)[a]	43.0 (11.24)	-	35.39 (12.76)	31.27 (15.4)	33.11 (18.2)
Estimated M	42.25	-	36.68	31.1	-

Observed and estimated means for the PHQ-9, GAD-7, BBQ and PPS from baseline to 3-month follow-up. The data are presented over time as means with standard deviations.
Baseline = before treatment start, Mid = middle of treatment, Post = after treatment, 3-months = post treatment end.
[a]Based on all non-missing data. Missing data ranges from 4–61% at specific timepoints.
[b]A significant effect of time, $p = 0.001$ was found in the model.
[c]A significant effect of time, $p < 0.001$ was found in the model.
[d]Not included in the model. Means and standard deviations for $n = 9$ participants included for descriptive purposes.

decreased by 62% during treatment, which corresponds to 32 h less gaming per week. Time spent gaming after treatment was on average 19.5 h per week which is well within the normal range according to Swedish Media Council (68). We want to emphasize that the aim of the treatment was not total abstinence from gaming or other internet activities but simply to gain control over gaming habits. With the gaming diary we also wanted to measure changes in non-gaming screen time, to make sure that time spent gaming not only transitioned into other types of screen-time. Instead, the gaming diary showed that the decrease in time spent gaming also was accompanied by a small decrease in other types of screen time. The patients also more than doubled their amount of screen-free leisure time. It is difficult to compare results from different studies as there are no gold-standard instruments for measuring GD, and many different instruments have been used in previous studies (69). With this caveat in mind, we observe that in our study, as well as in earlier studies regarding adults with IA (26, 28) and GD (23, 24), we see substantial changes in symptoms after treatment compared to baseline. This also holds for changes in hours spent online in our as well as in other studies (26, 28). In summary, this shows promise for using a CBT approach for treating GD.

Our secondary measures focused on anxiety, depression, quality of life, and procrastination. For these variables we saw changes in the expected direction, although the change in quality of life did not reach statistical significance. We argue that all these aspects are important to take into account when evaluating treatments for GD. By measuring for example quality of life we address a broader definition of health than simply the absence of symptoms, and capture additional aspects highly relevant to GD. Lower quality of life has been shown to be associated to GD, and also differentiating highly engaged gamers from those with problematic gaming (70, 71). The complex interplay between these factors is also illustrated by findings that levels of anxiety and depression mediate the relationship between GD and quality of life (72).

We also saw a significant reduction of symptoms of procrastination, measured by the PPS (53) after treatment, although the levels were still high. The decision to include strategies to identify and handle procrastination in our manual was based both on clinical observations, and earlier findings that symptoms of procrastination was associated with clinical severity of internet gaming disorder (73). Similarly, in a prevention program for adolescents with at risk for GD, a reduction of symptoms of GD was accompanied by a decrease in procrastination (74). The association between procrastination and GD is further supported by findings that lower levels of procrastination predict spontaneous remission of GD (75). Based on this we suggest that procrastination could be a relevant factor to take into consideration in treatment strategies for GD.

Limitations, implications, future research, and conclusions

Our study had some clear limitations but also strengths. There are a number of limitations in the dataset from this study: the sample size is small, there are missing data, there is no pre-treatment measurement for the primary outcome and a number of secondary outcomes, and repeated measurements have been given at variable time points (i.e., the gaming diary was not given every week during treatment but instead at specific sessions with varying amounts of time in between). The choice to collect the gaming diary more seldom than every week was made to minimize missing data. Still, a substantial amount of data was missing. In the coming randomized controlled trial (RCT) we will amend this by focusing more on collecting diaries on even fewer occasions during treatment, thereby being able to focus more on making sure that diaries on these chosen weeks will be registered.

The use of weekly diaries will still be part of the treatment, but our experiences so far indicate that, for a considerable part of the intended study population, remembering or wanting to complete these daily or weekly throughout the whole treatment period poses a challenge. Even though statistical methods (maximum likelihood estimation) have been employed to reduce the problem of missing data, the results of this pilot study should be interpreted with care. The single group design also limits the conclusions. These limitations will be corrected in a randomized controlled treatment study with follow-up at 3, 6, 12, 18 and 24 months (ClinicalTrials.gov NCT05328596).

There is a lack of treatment options and insufficient evidence regarding effective treatment of GD. This is the first treatment manual for GD, developed and studied in Sweden, closely evaluated with standardized measures and one of the few treatments so far developed specifically for GD. Moreover, our study participants have undergone a careful diagnostic assessment. This study is also highly clinically relevant as the participants are treatment seeking patients in regular care. Moreover, the patients have completed a follow up assessment 3 months after the treatment ended, which gives us a longitudinal indication of sustained effects. This is a strength since follow-up data after treatment is scarce (3, 21). Findings about the stability of GD over time are somewhat mixed. From studies to date it seems that a proportion of people with GD spontaneously recover (76) but a sizable amount remains that still fulfil the diagnosis at least one year later or more (66, 75). We also consider it a strength that we offer a flexible treatment, with additional sessions to add if needed.

To regain control over one's gaming behavior is challenging for all individuals and even harder for those with comorbid psychiatric disorders. We noted that almost 100% of the participants in our study had symptoms of psychiatric comorbidity with mood disorders as the most common one. A vast majority were men, not seldom isolated using the game to escape from negative thoughts and emotions.

Our CBT treatment, specifically designed to treat patients with GD, showed promising results with reduced symptoms of GD, upheld at least 3-months after treatment, accompanied by decreased time spent gaming almost equivalent to a normal work week. We further observed that the treatment was feasible to deliver as most patients stayed in treatment, and that the treatment was possible to implement as a part of regular care at the treatment center.

In conclusion, there is insufficient evidence regarding effective treatments for GD. Based on our promising preliminary pilot findings, we will conduct a RCT. For the upcoming RCT the manual will be shortened, giving increased possibilities to add sessions based on individual needs. We believe there is a need for a flexible treatment specifically designed for individuals with GD with considerable psychiatric comorbidity, to help them improve their quality of life and regain control over their gaming.

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 Swedish Ethical Review Authority. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AH had the main responsibility of the writing of the manuscript also contributed with specific knowledge in gaming addicted patients and the main idea for the manuscript. MM made all the statistical analyses and responsible for the result section. EA was responsible for the informed consent form to collect and keep track of the data and Method section. SL, JM, and AL developed the GOT-TO-GO manual and worked as the psychologists treating the patients in the study, reading the manuscript, and helped in writing the Method section. AS was a senior researcher of the work and the Principal investigator for this research, and supervised the writing of the whole manuscript throughout the research process. All authors contributed to the article and approved the submitted version.

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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

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Methylphenidate as a treatment option for substance use disorder: a transdiagnostic perspective

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A transition in viewing mental disorders from conditions defined as a set of unique characteristics to one of the quantitative variations on a collection of dimensions allows overlap between disorders. The overlap can be utilized to extend to treatment approaches. Here, we consider the overlap between attention-deficit/hyperactivity disorder and substance use disorder to probe the suitability to use methylphenidate as a treatment for substance use disorder. Both disorders are characterized by maladaptive goal-directed behavior, impaired cognitive control, hyperactive phasic dopaminergic neurotransmission in the striatum, prefrontal hypoactivation, and reduced frontal cortex gray matter volume/density. In addition, methylphenidate has been shown to improve cognitive control and normalize associated brain activation in substance use disorder patients and clinical trials have found methylphenidate to improve clinical outcomes. Despite the theoretical basis and promising, but preliminary, outcomes, many questions remain unanswered. Most prominent is whether all patients who are addicted to different substances may equally profit from methylphenidate treatment.

KEYWORDS

addiction, attention deficit hyperactivity disorder, psychopharmacology, methylphenidate (MPH), cognitive control

1. Introduction

Substance use disorder (SUD) is currently one of the most prominent mental disorders worldwide (1). According to the "World Drug Report" from 2019 by the United Nations Office on Drugs and Crime, around 36 million people suffer from SUD, which may be an underestimation, given that estimates for Europe reached 15 million cases of alcohol dependence alone in 2011 (2). The large scale of SUD occurrence bears an enormous burden to many individuals and society as a whole (3). For example, the current opioid epidemic leads to a rapidly increasing number of overdose deaths due to opioid misuse (4), and out of all brain disorders, alcohol use disorder is estimated to induce the third highest number of years of life lost (2). These numbers highlight the need for successful treatment of patients with SUD.

Existing treatments of SUD often fail to prevent relapse, and progress has been modest over the last 20 years. Only 17–35% of the individuals treated for alcohol use disorder (including pharmacotherapy, cognitive behavioral therapy, and group sessions) stayed abstinent for at least 1 year as reported in 2001 (5), while in 2016 a conservative estimate of 35% was obtained of SUD patients who can be considered in long-term remission (6). In addition, only a minority of SUD patients receive treatment. Development of effective prevention and cost-efficient novel treatment programs for SUD are, therefore, of significant importance, and alternative approaches should be explored.

New treatment approaches may stem from novel approaches to diagnose psychopathology. Specifically, the traditional categorical approach to psychopathology attempts to identify treatments based on maladaptive behavior and symptoms that characterize a disorder in a narrow sense by intentionally excluding overlap with other disorders. More concretely, a diagnosis for a given disorder is less likely when symptoms can be explained by another disorder. Therefore, the approach largely ignores behavioral and neural deficits shared by different disorders (7), thus potentially overlooking effective treatments. In contrast, contemporary approaches to diagnoses of mental disorders utilize various dimensions of symptoms within and across disorders. For example, deficits in executive functions may be characteristic of multiple mental disorders such as attention-deficit hyperactivity disorder (ADHD) and SUD [but also, among others, schizophrenia, autism, and Alzheimer's disease (1)]. This view is becoming more prevalent as it is acknowledged in the current version of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5; (1)]. Nonetheless, the DSM-5 can still be considered to be in a transitional period, as it does not fully endorse the view. Others take the dimensional approach further. For instance, the Research Domain Criteria project [RDoC; (8)] classifies disorders as quantitative variations on dimensions of a set of constructs (e.g., cognitive control) within domains (e.g., cognitive systems). These constructs are defined by elements that include behavioral performance, self-report, and biological mechanisms (c.f. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix). As these constructs can cut across mental disorders, we consider it reasonable that treatments follow suit by exploring treatments for seemingly different disorders that are similar in, at least some, underlying cognitive constructs and associated biological mechanisms. These shared deficits within the constructs can provide important opportunities for treatment (9, 10). Therefore, the potential of a pharmacological treatment to be used in SUD, but which is currently used for a disorder that shows similarities in the construct of cognitive control, should be explored.

Treatments for ADHD may be useful in SUD as both disorders are characterized by poor performance within the construct of cognitive control. The more specific aim of this study was to evaluate the potential of pharmacological ADHD treatment for successful use in SUD. At the core of the idea to utilize pharmacological treatment for ADHD in SUD lies the cognitive control deficit represented by inhibitory control failures as the most prominent (11, 12), which is shared between the two conditions (13) and the underlying dopaminergic dysfunction. In general, inhibitory control is the ability to suppress a prepotent or habitual response when necessary (14). When inhibitory control is lacking, actions are immediately and impulsively executed, often at the expense of long-term consequences, and with the disregard for long-term goals. These actions are inappropriate to the situation and are difficult to terminate once started. On a surface level, poor inhibitory control in SUD is demonstrated by displaying addiction behavior (e.g., consuming drugs), while rationally being aware that it is better not to do so given the long-term consequences (1). Similarly, in ADHD, poor impulse control is expressed by the inability to remain physically immobile and by frequent engagement in distractions (1). On the task-performance level, individuals with ADHD or SUD both perform poorly on laboratory measures of inhibitory control, such as the stop-signal task (SST) (11, 15). Lower response regulatory abilities have also been coined a risk factor for substance abuse (16). On a neurotransmitter level, dopamine (DA) receptor families play a prominent role in cognitive and inhibitory control (17), particularly deficient D2-like receptors are observed in individuals with high impulsivity (18). In addition, both ADHD and SUD patients show abnormal dopaminergic neurotransmission (18–20). Therefore, this transdiagnostic impairment in both ADHD and SUD suggests inhibitory control to be a suitable construct to investigate further as a target for pharmacological treatment (13). The potentially shared underlying neurobiological correlates should be explored to validate the pharmacological treatment. However, it should be noted that other disorders may share the neurobiological atypicalities as well as ADHD and SUD. Those disorders may not be suitable (e.g., schizophrenia) to be treated with typical ADHD medication. Therefore, the rationale presented below should be considered within the boundaries defined by the suitability of disorders to be treated with stimulant medication.

Existing pharmacotherapy for SUD does not appear to effectively target cognitive control (21). Nonetheless, neuropharmacological therapy is the most prominent treatment to target cognitive control deficits and deficient DA transmission in ADHD and is considered effective. DA-based ADHD interventions have a success rate of around 70% (1). While various stimulant drugs exist to treat ADHD, methylphenidate (MPH) is the most widely used and therefore, given the suggested overlap, can be considered a prime candidate for treating SUD. MPH blocks dopamine (DAT) and noradrenaline (NAT) transporters (22) and thereby increases extracellular DA and noradrenaline (NA) levels. MPH improves response inhibition task performance and reduces impulsive behavior in children with ADHD (23). MPH also has been shown to improve inhibitory control abilities in cocaine-dependent patients (24, 25), although this may be due to normalizing catecholamine levels by MPH in these particular patients. In addition, MPH has been considered safe with low addiction liability due to the slower onset and elimination of its effects (26). These findings suggest that MPH may successfully increase inhibitory control in SUD as it does in ADHD.

The purpose of this perspectives paper was to evaluate the potential for methylphenidate to be a suitable treatment option in SUD. By comparing ADHD and SUD on a (a) theoretical level, (b) behavioral/clinical level, and (c) neurobiological level, seemingly similar deficits are explored to assess the stimulant treatment's potential. Second, some direct evidence for the efficacy and effects of MPH in SUD treatment and criticism are reviewed, and finally, a guide is proposed for future research into knowledge gaps, ultimately to establish new treatments for SUD.

2. Evaluation of the hypothesis

2.1. ADHD and SUD overlap in theoretical models

Both theoretical models of ADHD and SUD attribute a central role to reduced or biased cognitive control of behavior. Currently, one hypothesis for the mechanism underlying ADHD characteristic

dysfunction is that low tonic catecholamine (DA, NE) activation leads to phasic hyper-responses causing distractibility, impulsivity, and disorganized thoughts (19, 27). ADHD is also associated with low prefrontal cortex (PFC) functioning, which causes reduced control over both external and internal stimuli, and reduced control of behavior. The PFC controls stimuli by dynamically inhibiting sensory cortices and subcortical structures. In ADHD, both structure and function of PFC are affected, reducing the ability to regulate information, which results in distractibility and impulsivity (28). This notion of core deficits in ADHD is supported by observations that the PFC, caudate, and cerebellum as a network are most prominently affected in ADHD (29, 30).

SUD is currently best explained by extended hypotheses that emphasize the increased value of potential rewards (31, 32) and increased habitual control of behavior (33, 34). The incentive salience/sensitization hypothesis states that stimuli that predict drug consumption cause an intense "wanting" of the drug, which is associated with a hyper-responsive mesolimbic DA system (31, 32). This response amplifies the motivational drive to obtain the predicted drug at the expense of long-term consequences and can, therefore, be considered biased goal-directed behavior. A second hypothesis that attempts to explain addiction behavior stresses reduced control over behavior, rendering goal-directed behavior habitual (33, 34). This transition is marked by a shift in brain activation from ventral striatum, indicating reward-based goal-directed behavior, to dorsal striatum, indicating fast, non-controlled behavior. While these hypotheses appear to differ in the way goal-directed behavior is affected (biased in incentive salience and reduced in goal-directed to habitual shift), both share a notion of a reduction in the weight of the behavioral choice to refrain from drug taking and thereby a relative lack of cognitive control directed at achieving long-term goals.

Taken together, both conditions are theorized to implicate insufficient or biased behavioral control governed by phasic catecholamine responses.

2.2. ADHD and SUD shared behavioral deficits

Impaired cognitive control as a broad term is often operationalized as various measurements of impulsivity. For example, the BIS-11 is an established self-report measurement of impulsivity (35). The scale consists of different subscales capturing aspects of inattention, spontaneous actions, lack of forethought, non-planning, and inhibition (36). More objective measures of impulsivity are provided by perseveration paradigms [e.g., Kertesz et al. (37)], antisaccade paradigms (38), conflicting or contralateral motor response tasks [e.g., Bellato et al. (39), Watson et al. (40)], go/no-go tasks [e.g., Trommer et al. (41)], and the stop-signal paradigm (42). All paradigms aim to assess the ability to inhibit prepotent responses. Antisaccade paradigms, conflicting and contralateral motor response tasks, go/no-go, and perseveration tasks all require the participant to withhold or change a response to a stimulus, whether the response is a saccade, eye-gaze, or a simple motor response like a button press. Perseveration paradigms are characterized by the need to change a response from a previously given response. Antisaccade paradigms require participants to make goal-directed saccades in the opposite direction to a presented stimulus, which elicits a reflexive saccade that needs to be suppressed. Similarly, a conflicting or contralateral motor response task requires the participant to make a spatial non-congruent response to a visual or tactile stimulus, e.g., in opposite direction to an indicated location. The go/no-go paradigm entails responding or withholding a cued response depending on the identity of the presented stimulus. Similarly, in the stop-signal task participants need to respond as fast as possible every time they see a target stimulus within a sequence of other insignificant stimuli (Go trials). However, when the target stimulus is presented together with a secondary cue, participants must refrain from responding (15). The difference between this paradigm and the former is that the secondary cue is presented after the imperative cue and therefore the stop-signal response time (SSRT) can be calculated, which enables quantification of the time needed to inhibit a response (43).

ADHD-diagnosed individuals show higher BIS-11 scores compared with matched controls (44), suggesting increased subjective impulsivity. Objectively assessed impulsivity is also increased in ADHD adults (45) as well as children (46, 47), particularly as assessed with the stop-signal task (46, 48). Up to 1,000 ms, slower inhibition of their responses compared with healthy controls has been observed (49, 50), while recent studies find smaller but significant differences between these groups (51). However, some studies report no group differences (52), which may be explained by the suggested ability of adults with ADHD to compensate for their deficits for a short amount of time (53). ADHD patients have shown impaired performance on antisaccade tasks compared with healthy controls, although the results are not unequivocal (54, 55). They also show lower scores on tests of perseveration [e.g., Houghton et al. (56), Fischer et al. (57)], conflicting motor response [e.g., Mahone et al. (58)], and on go/no-go paradigms (59).

Similar to ADHD individuals, SUD patients have shown high scores on the BIS-11 questionnaire indicating enhanced subjective impulsivity levels (60, 61). Various measures of brain structure and functions associated with inhibition failure have been shown to predict binge drinking during adolescence (62). Poor response inhibition abilities have also been shown to predict adolescent drug and alcohol use (63). More specifically concerning the SST, drug-dependent individuals show impaired performance on the SST. For example, individuals with cocaine use disorder have a lower probability of successfully inhibiting a response and do this more slowly compared with healthy controls (11). Furthermore, longer SSRTs can predict the degree of future alcohol consumption and progression toward dependence in heavy drinkers (60). Similarly, increased electrophysiological activation during SST performance predicts smoking cessation duration (64) and smoking behavior (65).

SUD patients have been found to display rigid response behavior by showing increased perseveration in a probabilistic reversal learning paradigm compared with healthy controls (66, 67). In addition, these differences could be reversed using the dopaminergic drugs pramipexole (66) and amisulpride (67).

TABLE 1 Qualitative summary of differences between patients with attention-deficit/hyperactivity disorder (ADHD) and healthy controls, and between patients with substance use disorder (SUD) and healthy controls on subjective and objective measures of impulsivity.

Tasks of impulsivity	Condition	
	ADHD	SUD
BIS-11	+	+
Perseveration	+	+/-
Antisaccade	+	+
Conflicting motor response	+	-
Go/no-go	+	+
Stop signal	+	+

+, presence of impairment; +/-, inconsistent findings; -, no observation of impairment.

A correlation between perseveration and duration of cocaine use has also been observed using an instrumental learning paradigm (68). However, perseveration did not differ from healthy controls in this particular study (68). In addition, increased perseveration in SUD patients has not been observed consistently across addictions (69). While cocaine users did show perseveration, chronic amphetamine and opioid users did not (70).

Nicotine-dependent individuals have been shown to perform worse compared with healthy controls on go/no-go paradigms (61), which is correlated with how much a person smokes per day (71). The poor performance on go/no-go paradigms has also been associated with relapse vulnerability (72). In addition, satiated smokers show impaired performance monitoring potentially contributing to the continuation of their smoking habits (73).

Adolescents at risk for developing an addiction show reduced antisaccadic performance (74) or a lack of performance improvement during adolescence (75), but which could be enhanced using incentives (76, 77). Performance on antisaccadic eye movements has been found to correlate with smoking status (71). Please see Table 1 for a qualitative summary of the behavioral observations.

To the best of our knowledge, there is one study comparing ADHD and SUD directly on objective measures of inhibitory control. Gerhardt et al. (78) observed more commission errors in ADHD subjects compared with alcohol use disorder subjects in a comprehensive paradigm assessing various cognitive aspects of impulsivity. However, they did not observe any behavioral differences on six other measures. Further direct comparisons that result in differences between the groups may argue against a common deficit. However, as presented above, both populations can be successfully discriminated from healthy controls using the BIS-11 (44, 60). In addition, similar cognitive control performance patterns already provide some objective evidence for similar inhibitory control deficits. Similar neural abnormalities might be responsible for the observed inhibition impairments and may strengthen this position.

2.3. ADHD and SUD shared neurobiological characteristics

Altered neurobiological metrics in both ADHD and SUD that form an overlap in brain areas that govern inhibitory control of behavior can be considered evidence for the shared deficits. Shared differences compared with neurotypical and healthy controls in neurotransmission, brain activation, and brain matter volume/density may exist. The aim of the following section is not to provide an exhaustive review of the neurobiological alterations in ADHD and SUD, but identification of overlap relevant to inhibitory control. Given that MPH targets catecholamine neurotransmission, shared catecholamine deficits should have the most weight in the evaluation.

2.3.1. Dopamine

DA plays a major role in the regulation of behavior, and small changes in DA levels impair cognitive control (29). Abnormal DA neurotransmission is one of the most important factors leading to behavioral dysfunction in ADHD (79, 80). Within the PFC–striatal–PFC loop, the "tonic–phasic DA hypothesis" of ADHD offers an explanation for characteristic ADHD symptoms (27, 81, 82). The model describes how a striatal imbalance between D1-like and D2-like receptor activation in patients with ADHD (79) affects the gating of PFC-striatal signals. The reduced gating ability leads to hyperresponsiveness of the individual. According to the model, normal striatal gating function is established by tonic extracellular DA concentrations that activate D2-like autoreceptors. This tonic DA-induced D2 receptor activation subsequently reduces phasic DA responses by a reduction in DA synthesis and release (81). In ADHD-affected individuals, low tonic striatal DA activity leads to decreased inhibition and subsequent increased phasic (burst of high level) DA signaling via striatal postsynaptic D1-like receptor activity (83, 84). Corresponding non-optimal receptor activation balance (19, 84) and low tonic/high phasic activation patterns (19) observed in individuals with ADHD support this view.

Increased DAT activity might underlie the observed D1-like/D2-like receptor activation imbalance (19). Elevated DAT levels accelerate DA reuptake and therefore reduce tonic D2-like receptor activation disinhibiting phasic activity. Multiple studies report heightened DAT levels in individuals with ADHD, which might be the result of inadequate neurodevelopment (23, 85, 86). These findings must be interpreted with caution because other studies do not confirm elevated DAT levels in ADHD patients (87). The inconsistent findings might originate from different inclusion criteria, methods, or screening techniques. Nonetheless, the most successful treatment for ADHD, MPH, blocks the DAT (88). DAT occupancy by MPH is positively correlated with reduced self-reported impulsivity (89). Therefore, whatever the neural deficit in ADHD, targeting DAT appears successful in ADHD treatment.

Taken together, while it is still unclear whether poor PFC functioning is the cause of low tonic DA activation in the striatum, and what role DAT activity plays in this, or whether increased phasic striatal output causes poor PFC functioning, it is clear that this PFC DA circuitry plays a prominent role in ADHD-related behavioral deficits (80). In favor of this view, stimulant-induced

enhancement of catecholamine function in the PFC of ADHD individuals is associated with behavioral improvements and can be reversed by noradrenergic α2 and DA D1 receptor antagonists (80).

Alterations in dopaminergic functioning have been observed in alcohol, cocaine, opioid, cannabis, and tobacco-addicted individuals (24, 90, 91) and have been well-studied using PET and SPECT (92). Drugs elicit high DA surges in the mesolimbic reward system (93). Tonic DA activity is suggested to be reduced to compensate for these excessive DA responses [(94), p. 104]. Cannabis users have shown reduced DA synthesis (95) and reduced striatal DA response following a stimulant challenge (96, 97), which might explain the lost interest for natural rewards and compulsive drug-seeking in SUD patients. Conversely, increased DA signaling has been observed subsequent to the presentation of addiction-related stimuli (98, 99) and D2/D3 antagonism reduced cue-induced responding and reward-obtaining impulsivity (100). In addition, reduced D2-like receptor availability has been observed (18, 91, 101), which correlates with age of cannabis use onset (97) and current use history (102). In addition, lower D2 receptor availability in the dorsal striatum in methamphetamine users predicted relapse (103). Lower D2-like receptor levels might underlie the observed hypofrontality and control impairments in SUD patients (104). A study showed that blocking D2-like receptors decreases prefrontal activity, especially in the IFG and anterior cingulate cortex (ACC), compared with participants receiving a placebo (104). The attenuated brain activation correlated with performance impairments in an SST. These findings confirm the regulatory function of DA in prefrontal inhibitory control mechanisms.

Concerning DAT availability, the many studies performed report inconsistent findings in SUD patients. Researchers argue for unchanged (105), increased (106), or decreased DAT densities (107, 108) in this population. Reduced DAT availability might be a reversible neuroadaptive response to the attenuated tonic DA activity observed in drug-dependent individuals (107, 109). When tonic DA levels are low, DAT may be downregulated to accommodate sufficient DA activity despite the lower levels. Contrariwise, increased DAT levels might be a failed attempt to compensate for extremely high DA levels following drug binges (23). It is of great clinical relevance to clarify DAT's role in addiction as many drugs, such as MPH, target these molecular complexes (93).

In conclusion, both ADHD and SUD are characterized by a hyperresponsive mesocortical DA system exerting increased phasic responding upon relevant (e.g., addiction associated) stimulation, which may be associated with reduced D2-like receptor function, low tonic DA, and altered DAT activity. However, findings concerning DAT levels are inconsistent for both conditions. For ADHD, the evidence appears to lean toward increased DAT levels whereas for SUD evidence points equally in both directions. Importantly, the mechanisms underlying the disorders differ, such that in SUD there may be an overall reduction in DA functioning leading to low tonic DA activation and low phasic activation in response to natural rewards, while only displaying high phasic activation to addiction-related stimuli. Conversely, in ADHD the low tonic activation is hypothesized to lead to high phasic activation toward a large number of different stimuli.

2.3.2. Brain activation

2.3.2.1. Mesolimbic system

The mesolimbic system plays a pivotal role in reward-based learning and incentive salience (110) and includes, most importantly, DA neurons in the ventral tegmental area and projections toward the nucleus accumbens. Exaggerated mesolimbic activity has been observed in animal models in which rats exhibit ADHD symptoms (111). However, only a few studies propose a hyperactive mesolimbic system in human individuals with ADHD, for example, when monetary rewards are presented to participants (112). Therefore, further research needs to clarify whether these functional deviations exist in human ADHD populations.

Mesolimbic neuroadaptations in SUD patients have been observed more frequently. Particularly relevant is the hyperactive mesolimbic reward system when addicted individuals are presented with drug-related cues [(113–115), see Leyton and Vezina (116); Berridge and Robinson (31) for nuanced views]. For example, alcohol-dependent drinkers show greater striatal activation in response to alcohol-related cues compared with social drinkers [(117), but see Vollstadt-Klein et al. (118) for conflicting results]. Following addiction-relevant cues, cocaine users (119), cannabis users (120, 121), alcohol-dependent patients (122–124), smokers [(125–127), but see Vollstadt-Klein et al. (128)], and cannabis users and heavy alcohol drinkers (129) all show increased frontostriatal activation (most often including nucleus accumbens) compared with neutral cues. The striatal response has also been associated with alcohol use problems (130) and, among other factors, the amount of alcohol used (131). This may reflect increased signaling of potentially high reward value and subsequent high motivation to obtain the substance of abuse (31). The high motivational drive may not be appropriately governed by frontal cortex circuits and ultimately leads to behavior strongly biased toward obtaining the substance.

Altogether, both ADHD and SUD individuals may show maladaptive mesolimbic processes. The high phasic DA-dependent striatal responses to environmental cues signaling potential rewards may lead to impulsive behavior. Ultimately, these maladaptive neuronal characteristics impair ADHD and SUD patients in their inhibitory control abilities and goal-directed behavior.

2.3.2.2. Cognitive control-related areas

Cognitive control is mainly mediated by an interaction between a frontoparietal network (14) and subcortical structures (132) in which DA plays a prominent role (133). Numerous dopaminergic connections between the subcortical areas and the PFC allow the inhibition of prepotent impulses (134). For example, frontal cortical "top-down" mechanisms inhibit subcortical "bottom-up" impulses via reciprocal connections (135), and the basal ganglia (e.g., striatum, subthalamic nucleus) can facilitate or inhibit frontal processes and therefore modulate behavior (136). Lesions in frontal areas can increase impulsive and disinhibited behavior (137), which is shown by several studies suggesting an association between frontal lobe functioning and performance on a response inhibition task (136, 138). Therefore, impulsive–compulsive disorders may be associated with frontal lobe functioning, which may occur in both

ADHD and SUD (109). As a number of studies report hypofrontality in both populations (136, 139), the extent of hypofrontality in both disorders may suggest a common brain-function deficit.

Functional imaging robustly supports prefrontal hypoactivity in individuals with ADHD. ADHD patients show attenuated activity in the ACC and dorsolateral prefrontal cortex (DLPFC), during cognitive task performance (140–142) and significant hypoactivity in inferior prefrontal and orbitofrontal cortices (OFC), striatum, thalamus, and parietal cortices (141). Decreased PFC activity is particularly evident in the performance of tasks that require sustained attention or inhibition of inappropriate movement (143). In addition, in an electrophysiological study, ADHD patients showed reduced activity in the superior frontal gyrus, which modulates self-control during the performance of a cognitive task, compared with controls (51). In support, transcranial direct current stimulation of the DLPFC can improve inhibitory control and reduces impulsivity in ADHD patients (140). That said, not all studies confirm these activation differences. For example, Dillo et al. (53) reported no prefrontal hypoactivity, but increased recruitment of attentional parietal areas. However, these findings may reflect less-efficient processing or compensatory strategies (52, 144) indicating non-optimal functioning.

From a brain network perspective, many of the brain areas that have been found hypoactive are part of the executive control network [ECN, (145)] consisting of the inferior frontal gyrus (IFG), ACC, pre-supplementary motor area (pre-SMA), DLPFC, anterior insula, and posterior parietal cortex (146–148). The ECN is hypoactive in individuals with ADHD during cognitive tasks (149). In addition, the PFC is less extensively connected with subcortical regions (139), which may lead to insufficient 'top-down' regulation of the default mode network [DMN, (150)] and the dorsal attention network (145). This was confirmed by observed disrupted functional connectivity between prefrontal control areas and regions of the DMN (151). In addition, task engagement should decrease DMN activation, but in children with ADHD, the network is activated during an inhibitory control task (52, 152). The disrupted interplay between the ECN and DMN might explain deficient control abilities in individuals with ADHD.

Frontal hypoactivation is also observed in SUD [(136), see Klugah-Brown et al. (153) for a meta-analysis]. For example, cocaine-dependent participants can be discriminated from healthy controls based on attenuated frontal activity during an SST (154). Especially areas of the ECN are affected, including, but not limited to, the IFG, ACC, and DLPFC (155, 156). Methamphetamine users showed reduced activation in brain areas associated with cognitive control (right IFG, supplementary motor area/ACC, and anterior insula) and performed worse than controls on a Stroop task (157). In further support, exciting the hypoactive DLPFC in SUD patients can improve decision-making and decreases craving (155). Furthermore, metabolism in the ACC and OFC is attenuated in individuals with SUD (155, 158), potentially contributing to reduced sensitivity to negative consequences of to-be-performed behavior (155, 159). However, these findings may reflect a neuronal vulnerability as deficient inhibitory control processes have been observed in non-consuming biological siblings as well as drug-dependent individuals (160), and white matter abnormalities are shared by first-degree biological relatives of SUD patients, who have no history of drug use (136).

One study directly compared brain activation of ADHD and alcohol use disorder patients as elicited by a comprehensive response inhibition task (78). Authors report more activation of a frontoparietal network, cortical and subcortical motor areas, and occipital areas in alcohol use disorder patients compared with ADHD patients. Taken together, while some activation differences seem to exist between SUD and ADHD patients, in comparison with healthy controls the hypoactivation of the ECN, and in particular the DLPFC, ACC, OFC, and inferior frontal gyrus, and the increase in cognitive control following DLPFC stimulation are shared between ADHD patients and SUD patients.

2.3.3. Gray matter

In addition to reduced activation, several imaging studies have shown that the DLPFC is smaller in patients with ADHD compared with controls (151, 161–164). Despite that whole brain reduction in thickness, volume, folding, and surface area have been observed (165), suggesting non-specific brain deficits, various measures converge on PFC deformation (28). Variations in dopamine D4 receptors (166, 167) are associated with thinning of PFC in ADHD (168) and reduction in DLPFC neuron density (169). In addition, PFC maturation has been observed to be slower in ADHD (167). Nonetheless, smaller caudate/putamen volume appears most prominent across various meta-analyses (28). These results support the earlier discussed potentially maladaptive prominent PFC–striatal–PFC network characteristics in ADHD patients.

In line with the idea of reduced cognitive control in SUD are the volumetric differences with healthy controls. A recent meta-analysis of 60 voxel-based morphometry studies shows reduced volume of the ACC, thalamus, and insula and increased putamen volume (170). This pattern of results is possibly reflective of decreased cognitive control and increased putamen (i.e., habits) governance of behavior. In addition, a large-scale analysis of gray matter volume in SUD patients has shown brainwide reduction in cortical thickness. While results were mostly driven by alcohol-dependent patients, thinning of OFC, inferior parietal, insula, and middle temporal cortices is shared across addictions to various substances (171). OFC plays an important role in value assignment to future rewards (172), damage to which leads to poor decision-making (173) and may help explain substance-biased behavior.

In summary, evidence for gray matter abnormalities in ADHD most strongly points to reduced DLPFC, while SUD appears best characterized by abnormalities of the OFC. Nonetheless, both structures are part of an executive control system governing reward-motivated behavior (174). ADHD and SUD appear to be differentiated concerning putamen volume, where smaller volume is observed in ADHD and larger in SUD. Please see Figure 1 for a qualitative overview of structural and functional differences between ADHD patients and healthy controls and between SUD patients and healthy controls.

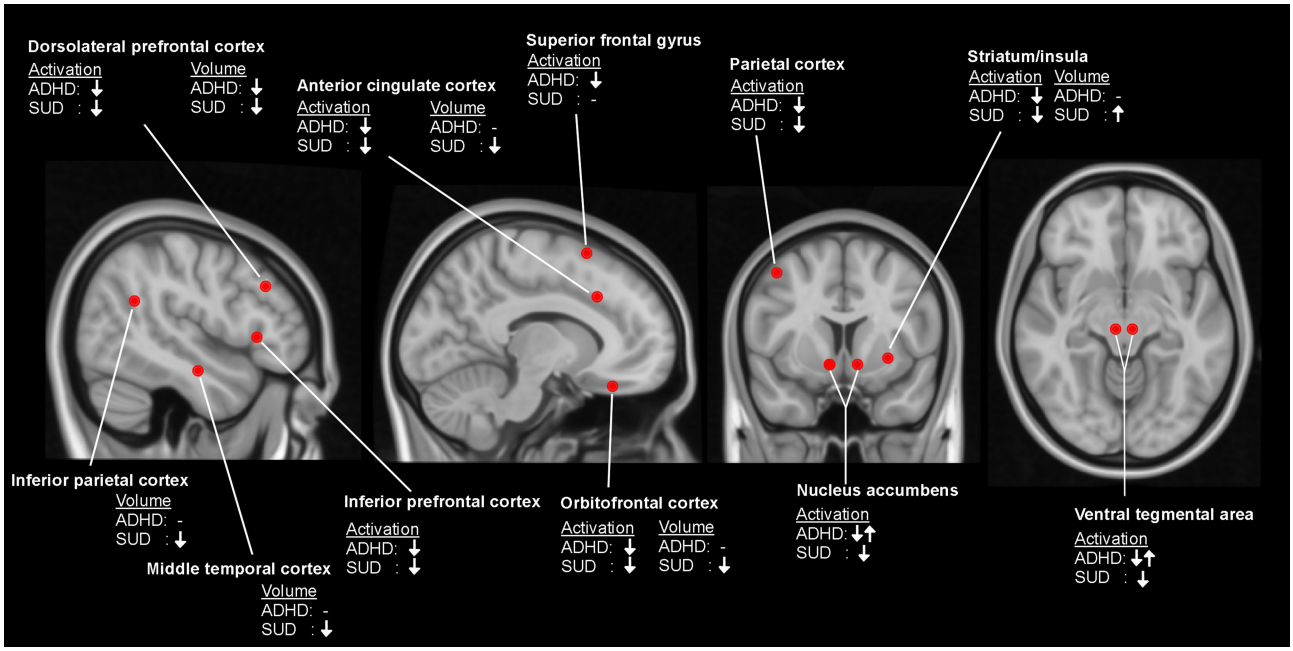

FIGURE 1
Qualitative overview of differences between patients with attention-deficit/hyperactivity disorder (ADHD) and healthy controls, and between patients with substance use disorder (SUD) and healthy controls in brain activation during performance of cognitive control tasks and measurements of local brain volume. ↓, reduced activation/volume; ↓↑, inconsistent findings; -, no observed difference.

2.4. Current evidence for MPH efficacy in SUD

Studies aimed at temporarily reversing neurobiological and behavioral deficits in SUD patients largely show that MPH is able to normalize brain function and task performance associated with three key deficits. First, concerning impulsivity, MPH has been shown to decrease stop-signal reaction time (SSRT) in cocaine users which correlated positively with middle FC activation and negatively with ventral medial PFC (25). A complementary analysis of the same data showed that MPH also restored [otherwise impaired (175)] activation in the ventral medial PFC before making commission errors on the stop-signal task (176). Similar findings of normalizing effects of MPH in cocaine users were observed for a cue reactivity task and ACC activation (24, 177, 178). Second, MPH improved cognitive control as shown by increased performance in both cocaine SUD patients and healthy controls on the Stroop task and selectively increasing DLPFC activation in SUD patients (179). Finally, hyperresponsiveness to drug-related cues was reduced by MPH in cocaine users (180).

Direct evidence for the efficacy of stimulants as treatment for SUD has been reviewed a number of times in the recent past. From these reviews emerges a view that MPH is the most, and perhaps the only (181), effective stimulant treatment [however see Dursteler et al. (182) for a nuanced view]. Two studies have shown higher abstinence rates from methamphetamine as a primary outcome after subchronic MPH administration compared with placebo [10–22 weeks; (183–185), but see Miles, Sheridan et al. (184)], as reviewed in Soares and Pereira (186). Ling, Chang et al. (183) observed approximately 15% positive urine drug screens after 14 weeks of MPH treatment vs. ∼34% for placebo. Moreso, in another but similar trial, the number of positive urine drug screens was also lower (∼20%) compared with placebo (∼35%) after 10 weeks of MPH treatment (185) or showed a reduced probability of being positive (187). In addition, MPH showed lower scores on measures of depression and craving (185), withdrawal symptoms, and addiction severity as secondary outcomes (186). Next to these studies, two other studies have shown favorable treatment outcomes of MPH in a sustained release formulation [(188, 189), reviewed in Lee et al. (190)]. After 10 weeks of MPH treatment, 46% of the urine tests were positive for the presence of amphetamine compared with 79% after placebo treatment (188). Finally, adding MPH to an existing behavioral therapy was superior in reducing craving and addiction severity, increasing mental health and number of negative urine tests than either treatments alone (191). Although MPH treatment remains to be refined (e.g., establishing dose–response curves in various SUD patient groups, with comorbidities, and with various addiction severities), these findings strongly suggest the potential value of MPH treatment. Please see Table 2 for an overview.

The neural mechanism from which these improvements may result remains unclear. Nonetheless, some data suggest that MPH reduces abnormally strong ventral to dorsal striatal functional connectivity in cocaine SUD patients, where addiction severity was associated with lower connectivity (197). These findings are in line with the prominent theory describing a ventral to dorsal striatal shift in the governance of behavior (33, 34). Another mechanism may be that MPH intervenes in assigning reward value to a drug experience. Evers et al. (198) observed that increased tonic dopamine activity by MPH reduced phasic ventral

TABLE 2 Qualitative overview of studies assessing the efficacy of methylphenidate treatment for substance use disorder.

References	MPH treatment	Primary outcomes. Executive functions/brain activation	Reported additional/side effects	Support
Goldstein et al. (24)	20 mg p.o.	Normalized ACC activation in cocaine users	- commission errors: ↓ - sleepiness: ↓ - performance confidence: ↑ - distrustfulness: ↓ - heart rate: ↑ - systolic and diastolic blood pressure: ↑	Yes
Goldstein and Volkow (178)	20 mg p.o.	Decreased commission errors on Stroop task, increased cdACC, rvACC/mOFC	- craving: ↓↑	Yes
Li et al. (25)	0.5 mg/kg i.v.	Decreased SSRT and restored brain activation in cocaine users.	- heart rate: ↑ - systolic and diastolic blood pressure: ↑ - euphoria: ↑ - anxiety: ↑ - cocaine craving: ↑	Yes
Matuskey et al. (176)	0.5 mg/kg i.v.	Restored brain activation in cocaine users	- heart rate: ↑ - systolic and diastolic blood pressure: ↑	Yes
Moeller et al. (179)	20 mg p.o.	Increased performance on Stroop task and increased DLPFC activation in cocaine users. Reduced ACC activation	- total errors: ↓ - post error slowing ↑	Yes
Volkow et al. (180)	20 mg p.o.	Reduced hyperresponsiveness of the limbic system to drug-related cues in cocaine users	- craving: ↓↑ - heart rate: ↑ - systolic blood pressure: ↑	Yes
		Abstinence		
Aryan et al. (191)	Month 1: 10 mg/day p.o.; Month 2: 7.5 mg/day p.o.; Month 3: 5 mg/day p.o.	Combined MPH and matrix Model treatment increased negative methamphetamine urine tests	- mental health: ↑ - craving: ↓ - addiction severity: ↓	Yes
Dursteler-MacFarland et al. (192)	60 mg/day p.o. for 12 weeks	No difference in negative drug tests	- reported cocaine use: ↓↑ - adverse effects: ↓↑	No
Grabowski et al. (193)	20/25 mg/day p.o. for 11 weeks	No difference in urine tests	- eating less: ↑ - more energy: ↑ - drowsiness: ↓ - jitteriness: ↑ - 'liking' (POMS): ↑ - blood pressure: ↑ - task performance: ↑ - craving: ↓↑	No
Levin et al. (194)	Titrated from 10 mg/day/p.o. to 40 mg/day p.o. to 80 mg/day p.o. in ADHD and opioid-dependent patients receiving methadone maintenance and 53% fulfilling cocaine dependence criteria	No difference in drug use	- compliance: ↓↑ - ADHD symptoms: ↓↑ - methadone maintenance: ↓↑ - fatigue: ↓↑ - sweating: ↓↑	No
Levin et al. (187)	Titrated from 10 mg/day/p.o. to 40 mg/day p.o. to 60 mg/day p.o. in cocaine-dependent ADHD patients for 14 weeks	Decreased probability of positive urine tests	- retention: ↓↑ - ADHD symptoms: ↓↑	Yes
Ling et al. (183)	Week 1: 18 mg/day p.o. Week 2: 36 mg/day p.o. Week 3-10: 54 mg/day p.o.	Fewer self-reported methamphetamine use days from baseline. No significant difference in number of positive urine drug screens at week 10, but less likely positive at week 14.	- cannabis positive drug screens: ↓ - craving: ↓ - retention: ↓↑ - adverse events: ↓↑ - treatment satisfaction: ↓↑	Yes

(Continued)

TABLE 2 (Continued)

References	MPH treatment	Primary outcomes. Executive functions/brain activation	Reported additional/side effects	Support
Miles et al. (184)	54 mg/day p.o. for 20 weeks	No different abstinence from methamphetamine rates compared with placebo	- retention: ↑ - craving: ↓↑ - severity of dependence: ↓↑	No
Minarik et al. (189)	Individual titration from 20 mg to 60 mg/day p.o. for 8 months	10 cases of abstinence out of 24 cases	- one case of alcohol poisoning - quality of life: ↑ - health conditions: ↑	Yes
Noroozi et al. (195)	60 mg/day p.o. for 12 weeks	No difference in negative urine tests	- craving: ↓↑ - withdrawal: ↓↑ - addiction severity: ↓↑ - depression: ↓↑ - high-risk behaviors: ↓↑	No
Rezaei et al. (185)	Week 1: 18 mg/day p.o.; Week 2: 36 mg/day p.o.; Week 3–10: 54 mg/day p.o.	Higher abstinence from methamphetamine rates	- craving: ↓ - depression score: ↓ - adverse events: ↓↑	Yes
Schubiner et al. (196)	Titrated from 30 mg/day p.o. to 60 mg/day p.o. to 90 mg/day p.o. for 12 weeks in cocaine users with ADHD	No difference in reported cocaine use or money spent on cocaine	- retention: ↓↑ - insomnia: ↑ - sadness: ↑ - single case of hypertension - single case of disorientation, insomnia, and anxiety - inattentive symptoms: ↓↑ - hyperactive symptoms: ↓ - craving: ↓↑	No
Tiihonen et al. (188)	Week 1: 18 mg/day p.o.; Week 2: 36 mg/day p.o.; Week 3–20: 54 mg/day p.o.	Fewer positive urine tests for amphetamine compared with placebo	- retention: ↓↑	Yes

↓, decrease; ↑, increase; ↓↑, mixed findings; p.o., per os; i.v., intravenous.

striatal response upon receiving reward. MPH may therefore suppress reward value and diminish reward-based learning in SUD patients, which is in line with an MPH-induced reduction in functional connectivity between the nucleus accumbens and ventral pallidum (199) as a neural substrate for drug liking (200). Improved behavioral control is suggested by MPH-induced altered functional connectivity between the nucleus accumbens medial PFC (199), an area associated with reflective cognition (201). In addition, MPH reversed an acute stress-induced reduction in brain activation associated with goal-directed behavior (202). Taken together, these data suggest MPH to increase behavioral control at times of choosing to perform a particular behavior associated with consequences including drug-related reward, an ability that may be key in maintaining abstinence.

2.5. Criticism

Despite the promising results, some criticism exists that needs to be considered. For example, cocaine users report increased drug wanting after MPH when prompted by relevant situations (203). MPH has also been shown to enhance the reinforcing effects of amphetamines in mice (204), and increase smoking behavior in neurotypical (205) and ADHD patients (206). Such effects would be counterproductive in a treatment setting. It should be noted that participants in both latter studies did not intend to quit smoking.

MPH-based treatment may also not be effective in some other addiction populations (186). For example, pathological gamblers have been shown to increase their motivation to gamble (207) and show increased DA release in dorsal striatal structures following amphetamine administration (208). The latter may contrast methamphetamine users in whom low levels of dorsal striatal DA release predict relapse (103) and in which MPH has shown to be effective the most. Another potential subgroup of SUD patients is formed by ADHD patients. There is a high comorbidity between ADHD and SUD (209, 210) for which various explanations exist. For example, individuals with undiagnosed ADHD may self-medicate with stimulants in an attempt to alleviate the symptoms (211). ADHD individuals also may be inherently vulnerable to SUD due to impulsive behavior and neurobiological characteristics (210). Subsequently, the proportion of ADHD patients in the SUD population is relatively large. The evidence for the efficacy of MPH to treat SUD in this particular population is limited, as many of these patients are already treated with MPH while SUD is still present [c.f. Wilens and Morrison (211)]. Crunelle et al. (89) detected that the limited success of MPH in cocaine-using ADHD patients compared with an ADHD-only group did not correlate with lower DAT occupancy. In addition, the effect of MPH is compromised in ADHD patients with comorbid cocaine dependence (196). On the other hand, MPH treatment of ADHD children has been shown to reduce the risk of substance (ab)use during adolescence (212). Therefore, individuals presenting with comorbidity at a later age may be predominantly more treatment

resilient. It should be considered that the population with such comorbidity may require a different treatment approach.

Results of studies assessing the efficacy of MPH in the SUD population are not unequivocal (186), with some large, well-designed studies showing no difference between MPH treatment and placebo [e.g., Noroozi et al. (195)]. In addition, Dursteler et al. (182) report negative findings concerning the efficacy of MPH as a replacement medication in patients with cocaine use disorder specifically in five randomized controlled trials (187, 192–194, 196). However, these studies did not form a homogenous group. Differences between the studies exist as some studies included patients with ADHD and others did not. Other differences were the use of concomitant medication, duration of treatment, and dose of MPH. All the above criticisms could be considered a starting point for determining boundary conditions in which MPH may be effective; e.g., in which populations and with which doses may MPH be most effective?

Another potential limitation to the use of MPH as treatment is its abuse potential and associated health risk. Abuse potential may be suggested by observed behavioral cross-sensitization with amphetamine (213), increased drug-seeking behavior (204), and conditioned place preference (214) in rodents. The abuse potential may also be signaled by the abundant use among the student population (215), which may be associated with the risk of cardiac disease (216). Moreover, MPH has been ranked 12th on a list of substances causing physical harm (217). However, most studies in humans have not observed reinforcing effects of MPH using clinical oral doses [for an overview see Kapur (218)]. In addition, conditioned place preference for orally administered MPH was only observed for higher doses or when administered immediately before testing (214). The slow onset of effects of orally administered MPH [in contrast to intranasal administration (219)] and its slow clearance have also been associated with reduced abuse potential compared with that of other stimulants (220). In conclusion, misuse of MPH is observed and is associated with health risks. However, potential clinical use to treat SUD may be safe in clinical oral doses and when closely monitored to guard against abuse.

One of the pillars of the current argument is that hypofrontality is characteristic of impaired inhibitory control and is shared by ADHD and SUD. However, hypofrontality is not exclusive to ADHD and SUD but also occurs in schizophrenia (221), bipolar disorder (222), and major depressive disorder (223). Therefore, the fact that ADHD and SUD share this characteristic is insufficient to treat both with the same pharmacological agent, as this is clearly undesirable in, for example, schizophrenia. In addition, the functional interplay between frontal and striatal areas underlies working memory, attentional function, and task-switching performance (224) as well as response inhibition, which means that hypofrontality alone cannot be considered evidence of impaired inhibitory control specifically. Therefore, shared hypofrontality in isolation should not be considered conclusive evidence of similarities between the disorders in inhibitory control deficits. Instead, it should be considered in conjunction with the overlap in theoretical models, and behavioral and, most importantly, DA deficits.

3. Discussion

The primary objective of this paper was to explore shared behavioral and neurobiological atypicalities between ADHD and SUD to evaluate the potential usefulness of MPH treatment for SUD. Overlap between disorders can be considered based on their independent explanatory hypotheses stating impaired or biased cognitive control. Empirically, both show inhibitory behavior deficits as subjectively and objectively measured using the BIS-11, and SST, antisaccade, perseveration, conflicting motor response, and go/no-go paradigms. Functionally, they both show hyperactivation of the mesolimbic pathways, albeit for ADHD only in animal models. Atypical neurotransmission is shared by both disorders characterized by low tonic DA signaling and higher phasic response given appropriate stimuli. Finally, behavioral control networks, including frontal gyri, ACC, OFC, and DLPFC (53, 155), and frontal gray matter is prominently compromised in both disorders, which is in line with the behavioral deficits. These observations support the application of DA-based stimulants as a treatment for SUD, and current evidence identifies MPH as the main candidate among other stimulants.

Despite the shared characteristics, there are differences between ADHD and SUD patients. For example, a prominent ADHD symptom is inattentiveness, which is not commonly observed in SUD individuals (1). In addition, SUD individuals' impulsive behavior appears to be restricted to responding to drug-related cues, whereas ADHD patients behave disinhibited regardless of the context (60). For example, ADHD individuals show increased reward-circuit response during a monetary incentive task (112), while SUD patients often show a reduced response [e.g., Luijten et al. (225)]. ADHD patients commonly use compensatory strategies involving parietal attention areas to mask their cognitive deficits, while SUD patients do not show these additional activity patterns (53). Until now, only individuals with ADHD show unusual activity patterns in the DMN and the OFC is dysfunctional primarily in SUD patients (101, 151). Structural differences between these populations are also present with putamen having been shown to be enlarged (170) in SUD, but decreased in ADHD (28). Important for the present purpose of evaluating MPH suitability as a treatment for SUD, DA-related characteristics in ADHD appear to be mostly represented by high levels of DAT (85, 86), while results for SUD are inconsistent. As MPH blocks the DAT, similar characteristics may be desired. However, both conditions share low tonic DA and high phasic DA (79, 226) that may be reversed using MPH regardless of the DAT differences.

Future studies should be aimed at clarifying apparent discrepancies, behavioral relevance of neurobiological and neurofunctional atypicalities, and the effects of MPH on these measures of performance. For example, on a behavioral level studies may directly compare ADHD and SUD individuals on BIS-11 scores and SST performance. It may be established whether both populations differ to an equal extent from neurotypical, healthy controls. Performance on the SST may also be subject to boundary conditions. For example, it should be established whether SUD individuals only show higher SSRT when presented with addiction-relevant cues or whether they are impaired across

a variety of task conditions. Such knowledge can aid in designing situation-specific treatments.

In addition to behavior, further direct comparisons between the populations should also be made concerning brain activation [e.g., Gerhardt et al. (78)]. The key questions that need to be answered are (1) whether ADHD and SUD individuals show similar altered responses of brain networks governing behavioral control, and if so, (2) are hypofunctional frontal brain areas equally relevant in both disorders for behavioral control specifically? (3) What is the contribution of other executive function deficits to the maintenance of the disorders? Multiple executive functions are impaired in both groups, e.g., reward processing, and further studies should establish similarities between the disorders and the effects of stimulant treatment of these functions (49). These functions can be assessed using various well-established performance tasks addressing different aspects of behavioral control like SST assessing motor control (42), gambling tasks assessing reward learning (227), and devaluation tasks assessing goal-directed behavior (228). Concerning the latter, and in parallel to the theory that addiction is characterized by a transition from goal-directed toward habitual behavior, a direct comparison would be very valuable to determine whether ADHD individuals show a similar shift in activation of brain areas governing goal-directed/habitual behavior as is often observed in SUD individuals [e.g., Sjoerds et al. (229)]. In addition, future studies may investigate whether factors that are known to elicit habitual behavior [e.g., stress, Schwabe and Wolf (230)] are equally effective in these populations in affecting brain activation and associated goal-directed behavior.

Further key questions concern explaining the inconsistent observations of DAT levels in SUD. For example, it may be argued that if DAT levels are a consequence of drug use, different drugs may affect DAT levels to a different extent. Drugs exerting their effects through strong activation of catecholaminergic neurotransmission (e.g., amphetamine, cocaine) may induce downregulation of DAT, while drugs like cannabis and heroin may do this to a lesser extent. Within that context, most evidence for the efficacy of MPH in SUD comes from studies in stimulant use disorder patients. It appears reasonable that SUD involving catecholaminergic drugs (e.g., cocaine, amphetamine) may benefit most from MPH treatment. It remains an empirical question whether all addictive disorders are equally suitable to be treated with MPH. It is assumed that all addictions share underlying neurobiological alterations, and based on that notion, it can be hypothesized that MPH is potentially effective in all forms of addiction. However, such extrapolation should be made carefully and awaits empirical confirmation, as most studies showing efficacy in SUD only concern stimulant use disorder patients.

If subpopulations within SUD can be identified, treatments may be tailored to these groups such that MPH treatment may be suitable for one but not the other group or that different dosages may be needed. As well as SUD subgroups, ADHD subgroups (inattentive, impulsive, combined) should be considered. It may be predicted that the impulsive type shares most behavioral and neurobiological characteristics compared with the inattentive type. However, the efficacy of MPH in potential subgroups remains an empirical question that future studies should answer.

Another characterization that may define a suitable subpopulation of patients may be neuroimaging measures of the dopamine system. For example, cocaine-dependent patients that show high D2/3 receptor binding and dopamine release following MPH choose a monetary incentive over cocaine more often compared with patients showing less D2/3 binding and dopamine release (231). Such methods may even be hypothesized to assess sensitivity to treatment effects on an individual level. It has been argued that individual tonic dopamine levels are associated with the clinical effectiveness of treatments (21). Such variability in tonic dopamine levels can further be utilized to define individual treatment needs. For example, monetary rewards can be an effective reward for cocaine (231, 232) and smoking (233) abstinence. It is an outstanding hypothesis that the level of dopamine responding to MPH or D2/3 receptor binding can define the height of the monetary incentive, such that lower dopamine system level responding requires larger rewards. In conclusion, more detailed information concerning subgroups, individual differences, and other boundary conditions is needed to determine the suitability of MPH in treating SUD.

The current paper is limited in its scope in evaluating the potential use of MPH as treatment for SUD. Nonetheless, alternative approaches to treating SUD should be considered. Thus far, part of the rationale presented in the current paper to treat SUD patients with MPH is based on a current theoretical explanation of addiction (31, 32). Addiction-related cues elicit a DA response in the ventral striatum, which is associated with an intense craving ("wanting") of the drug. MPH is theorized to be able to reduce the phasic DA response and therefore the craving. An alternative approach to the function of DA and the mesolimbic system is one in which the system provides a learning signal whenever a reward is larger than predicted [reward-prediction error; (234)]. This signal aims to strengthen the association between the stimulus, response, and outcome (235). In rodents (236) and humans (237, 238), high doses of nicotine have been observed to enhance this signal, which may consequently continue the learning of and strengthen the associations between smoking cigarettes and obtaining reward. An effective treatment may be the dampening of the DA signal whenever a cigarette is smoked to reduce the positive reward-prediction error. MPH has been shown to reduce ventral striatal activation in response to receiving a reward (198). In addition, psilocybin (a hallucinogenic substance found in "magic mushrooms") may also reduce phasic DA neurotransmission in the mesolimbic pathway. Psilocybin is a 5-HT2A agonist, which predominantly is expressed in the mesolimbic pathways. There is consensus that 5-HT2A activation inhibits DA release (239). Therefore, it can be hypothesized that psilocybin administration leads to a reduced positive reward-prediction error and the association between substance taking and reward. Future, studies should test these hypotheses derived from this rationale.

Concerning alternative approaches, non-invasive brain stimulation or neurofeedback increases prefrontal activity, reduces impulsivity, and enhances cognitive functions (14, 88, 140) and may therefore be considered a potential treatment. In addition, for drug-dependent individuals it is important to train psychosocial

skills alongside pharmacological treatment to ensure abstinence. Learning new coping skills, developing a new support system, and challenging expectations about drugs are important factors that enhance self-regulation abilities (156).

Taken together, this perspectives paper provides evidence toward a dimensional approach of psychopathology and serves as an illustration for the promise of developing transdiagnostic treatment programs. More specifically, it contributes to the development of novel pharmacological treatment approaches that may be based on treatments for disorders that are similar in underlying etiology (9). The transdiagnostic symptoms of disinhibition and impulsivity that are characteristic of both SUD and ADHD may have overlapping underlying etiology, namely, abnormal tonic/high phasic DA transmission that leads to a strong drive to perform a given action. This behavior may be associated with prefrontal hypoactivity and brain structural deficits. The DA transmission deficit can be treated with MPH, which has been proven successful in ADHD and may be suitable for use in SUD. The key question is whether the maladaptive behaviors in ADHD that can be treated with MPH are indeed resulting from the DA atypicalities that are shared by both conditions. Also, it is clear that ADHD and SUD are not the same, and it should be studied whether the neurobiological differences underlie other aspects of the respective phenotypes.

Author contributions

PR and LF contributed to establish the first draft of the manuscript and contributed to developing the rationale. LF summarized the existing studies. PR wrote the first draft of the manuscript. NM, JR, and PS contributed to the manuscript in its current version. 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.

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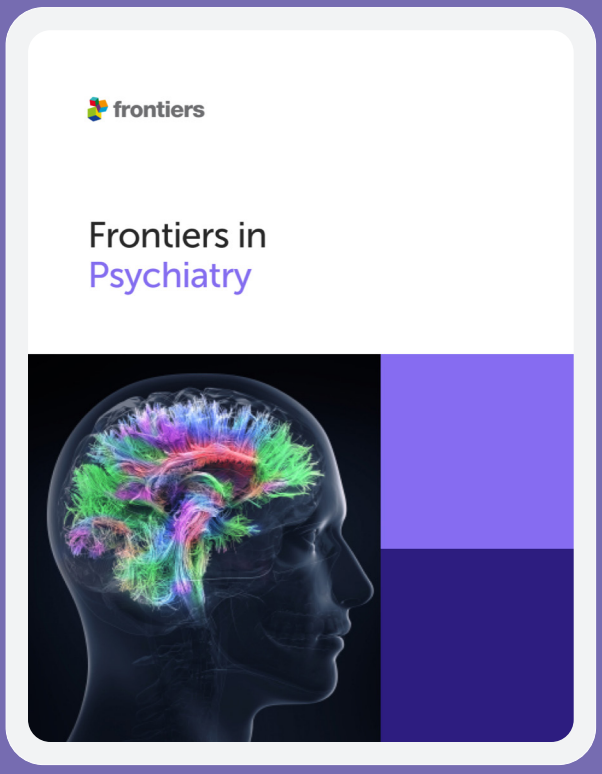

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