COMORBIDITY OF SUBSTANCE USE DISORDERS WITH MENTAL HEALTH DISORDERS

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COMORBIDITY OF SUBSTANCE USE DISORDERS WITH MENTAL HEALTH DISORDERS

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Table of Contents

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Relationship Between Personality Disorders Scales, Pathological Personality Traits, and Six Domains of Functioning in Sample With Alcohol Use Disorder

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Background: Studies reveal a functional impairment in patients with personality disorders (PDs), but there is not enough information to form conclusions about this relation in patients with alcohol use disorder (AUD). The aim of this study was to investigate to what extent a personality disorders scales including pathological personality traits (PPTs) predict six domains of functioning in patients with AUD.

Methods: In total, 48 patients with AUD diagnosis, who were treated in the psychiatric clinics, aged 20 to 65 years [M = 37.5; SD = 12.08; 12 (25%) females and 36 (75%) males], filled out the demographic questionnaire, WHO Disability Assessment Schedule 2.0 (WHODAS 2.0, Latvian version) and Latvian Clinical Personality Inventory (LCPI v2.1.). All respondents signed the informed consent form.

Results: Stepwise regression analysis showed that PD Avoidant scale positively predicts impairment in Cognition and Getting along domains of functioning in AUD patients, but, on the PPTs level, it was found that Social withdrawal along with Irresponsibility and Guilt/Shame positively predict impairment in Cognition domain of functioning, and Social withdrawal along with Depressivity and Irresponsibility positively predict impairment in Getting along domain of functioning. The results of the study showed that PPT Orderliness negatively predicts impairment in Live activities domain of functioning. The PD Dependent scale and PPT Separation insecurity positively predict impairment in Participation domain of functioning.

Conclusions: Obtained results add deeper insight into understanding of the relationship between personality disorders scales including pathological personality traits and six domains of functioning in patients with AUD.

Keywords: alcohol use disorder, functioning, Latvian Clinical Personality Inventory, personality disorders, pathological personality traits

INTRODUCTION

According to the World Health Organization (further—WHO), more than three million people worldwide die as a result of alcohol use. Alcohol misuse accounts for more than 5% of the global disease burden (1). The use of alcohol in Europe's regions is the highest in the world and remains a serious public health problem, causing Alcohol Use Disorder (further—AUD) and the consequences that hinder a person's ability in key areas of life (2, 3). The incidence of AUD in the population aged 15 and over in Latvia in 2016 is 10.4%, which is 3.7% times higher compared to European regions as a whole (1). As noted in a study by the Latvian Center for Disease Prevention and Control in 2017, the number of first-time patients with alcohol dependence in absolute numbers was 1,634 patients, of whom 1,194 were men and 440 were women (4).

Functional consequences of AUD create high probability of impairing functioning in the major areas of life, such as interpersonal relationships, and contributes to disinhibition and feelings of sadness and irritability (5), lack of self-cognition and social competences (6, 7), and difficulty in dealing with everyday problems (8). The results of recent studies indicate that those with AUD have an impairment in the domains of Participation in the society, household, and work-related activities as well as cognitive functioning, and also, some functional impairment is recorded in the domains of Mobility and Self-care (9, 10).

Research has consistently shown that AUD patients have high rates of psychiatric comorbidity (11). AUD is characterized by clinical, genetic and neurophysiological heterogeneity that is closely related to other mental disorders (12), for instance, anxiety, depressive, bipolar disorders, schizophrenia, and personality disorders (further—PDs) (13–17). PDs are four times more common among addictive and psychiatric patients compared to the general population (14).

AUD Comorbidity With Personality Disorders and Functioning Impairment

PDs are made up of a group of psychiatric disorders that all share a common feature of an enduring, maladaptive behavior pattern markedly deviating from social expectations from individual's culture, which is pervasive and inflexible, stable over time, and leads to distress or impairment (5). As concluded in studies, PDs in alcohol addicted patients prevail up to 58–78%, besides, in literature there are often mentioned B-cluster disorders, especially borderline and antisocial PD (3, 18, 19). However, alcohol-dependent individuals have a whole spectrum of PDs, including avoidable, paranoid, dependent, and other PDs (13).

It is known that individuals with any PDs had greater impairment in instrumental role functioning in the previous 30 days, as assessed by days out of role, productive role functioning, and social role functioning (odds ratios 1.5, 1.6, and 2.0, respectively), adjusting for sociodemographic characteristics and Axis I disorders. Having a Cluster B PDs were strongly associated with impairment in social role functioning (OR 2.7) (20), for instance, individuals with borderline PD are likely to experience marked functional impairment, particularly in the social domain (21). Other research findings confirm that schizotypal and borderline PDs were significantly related to impairment at work, in social relationships and at leisure (22). There is also evidence from longitudinal studies that PDs are associated with future impairment. On the one hand, research reveals functional impairment in patients with PDs, but on the other hand, there is not enough information to form conclusions about such relation in patients with AUD.

DSM-5 Dimensional Approach to PDs Diagnosis

Researchers pointed to the need to revise the diagnostic approach to PDs concerning high rates of comorbidity, the heterogeneity, observed among patients with the same diagnosis, and poor grounding of the cut-off points for differential diagnosis (23, 24). There are developed several dimensional models of personality pathology (25), one such model is described in DSM-5 (DSM-5 Trait model) (5). In the III section of the DSM-5, there is offered an alternative hybrid approach to PDs diagnostics, which combines both the categorical approach, based on the determination of the severity of the combined personality dysfunction, and the dimensional approach that allows obtaining the unique personality trait profile of a particular individual in PDs diagnostics (25). In this model, PDs are "characterized by impairments in personality functioning and pathological personality traits" [(5), p.761]. Despite the slightly differing views of experts about which pathological personality traits (PPTs) are most relevant and characterise particular PD [see (5, 26)], this approach could be very useful in clinical practice.

Pathological Personality Traits in Patients With AUD

Studies have shown that the most frequent PPTs associated with alcohol abuse are impulsivity, neuroticism, negative affectivity (27, 28) and narcissism (29). Intense anger, impulsivity, and mood swings are characteristic both in case of alcohol addiction and for borderline personalities (18). Given this latest and reasoned hybrid approach to PD diagnostics, it would be important to find out what is the relationship not only between PDs with functioning impairment for AUD patients, but also with PPTs.

Pathological Personality Traits and Functioning Impairment in Patients With AUD

In the study (30) which explored the relationship between the personality traits and six domains of the WHO Disability Assessment Schedule, WHODAS 2.0 (further—WHODAS) (5) in patients with dual diagnosis, there were found significant correlations between all functional domains and Anxiousness and Depressivity. The domain of Cognition shows correlations with Perceptual Dysregulation and Distractibility, the domain of Participation in society shows moderate correlations with Unusual Beliefs and Anxiousness. The domains of Getting

along with people and Life activities show moderate correlations with Anhedonia, Eccentricity, and Irresponsibility.

It can be concluded that the research of PDs in connection with the difficulty of functioning in people with AUD may lead to superficial and limited conclusions, if the traits of abnormal personality are not analyzed in addition.

The aim of this study was to investigate the extent to what PDs including PPTs scales predict six domains of functioning in patients with AUD.

METHODS

Participants

It was a cross-sectional (simultaneous) study with the target group defined as patients in psychiatric hospitals who were diagnosed with F10.2: Alcohol Dependence Syndrome based on ICD-10 (31). Criteria for inclusion in the particular study were: AUD diagnosis (F10.2.); Latvian is the native language; aged past 18; signed informed consent to participate. Criteria for exclusion were: assigned disability group; diagnosed other mental disorders of Axis I (31); time after detoxification therapy less than 14 days.

From 180 patients of the psychiatric hospitals who signed informed consent to participate in the initial stage of validation study, 48 patients were recognized as meeting the above mentioned criteria and were selected for inclusion in the sample of this study. These patients were aged 20 to 65 years (M = 37.5; SD = 12.08), 12 (25%) were females and 36 (75%) were males. All patients included in the study were treated in the programs which are based on the Minnesota Model approach. None of those involved in the study had a diagnosis of PDs and behavioral disorders in adults (F60-F69) by ICD-10 (31).

Measures

The survey packet consisted of 707 items in total divided in the three parts: 1) demographic questions (7 items), 2) the World Health Organization Disability Assessment Schedule (WHODAS 2.0) (36 items), and 3) the Latvian Clinical Personality Inventory version 2.1. (LCPI v2.1.) (664 items).

The first part included demographic questions about age, gender, native language, mental health, time after detoxification therapy, and disability group.

The second part was the WHODAS 2.0 (32), adapted in Latvia by Bērziņa, 2016 (33), which is a generic assessment instrument for health and disability, a tool to produce standardized disability levels and profiles, applicable across cultures, in all adult populations, directly linked at the level of the concepts to the ICF. It contains 36 items and six domains: Cognition, Mobility, Self-care, Getting along, Life activities, and Participation (Cronbach's alpha varied from 0.81 to 0.93). It measures the ability of functioning and daily activity over the last 30 days and difficulties or incapacity associated with dysfunction.

The third part was the preliminary version of the Latvian Clinical Personality Inventory version 2.1. (LCPI v2.1.) (34). LCPI v2.1. consists of 664 true-false items. In the present study, there were used only 10 scales of personality disorders (PDs) (Schizotypal, Schizoid, Paranoid, Histrionic, Narcissistic, Antisocial, Borderline, Avoidant, Dependent, and Compulsive) and 34 facet-level scales of PPTs. All the 10 scales of PDs and 34 PPT scales show acceptable to high internal consistency (for PDs scales Cronbach's alpha varied from 0.68 to 0.90 and for PPTs scales Cronbach's alpha varied from 0.67 to 0.90) (35).

Data Collection

Data were collected from December 2016 to February 2017. All procedures were approved by the Riga Stradiņš University Ethical board. Data were collected by meeting each patient with AUD individually. All patients signed the informed consent form. During the testing session, patients filled out the demographic questionnaire, LCPI version 2.1, WHODAS 2.0. The confidentiality of respondents was fully respected in data collection and processing. Only valid protocols (based on the LCPI Validity scales) were used in this study. This study formed part of a LCPI-v3 development and validation research carried within the framework of Latvian National Research Programme Biomedicine for Public Health (BIOMEDICINE) 2014–2017 (sub-project Nr.5.8.2).

Data Analysis

For the processing and analysis of the data, SPSS software v.20.0 was used. To investigate the relationships between WHODAS domains, PDs scales and PPTs, the Spearman's rank correlation method was used. Simple and multiple stepwise linear regression analysis was conducted to find out which PDs and PPTs are predictive for functioning impairment. R^2 change effect sizes were interpreted by Cohen (36) conventions (change effects of .01, .06, and .14 were interpreted as small, medium, and large, respectively). For power analysis (to determine the probability of detecting a "true" effect when it exists), G*Power version 3.1.9.2. (37) was used.

RESULTS

In the first stage of data analysis, there were analyzed relationships between WHODAS domains both with PDs and PPTs scales. The obtained results are shown in the **Tables 1** and **2**.

It was found that 4 of 10 PDs (Paranoid, Antisocial, Histrionic, and Narcissistic) show no statistically significant correlations with any of six domains of functioning. Obsessive-Compulsive PD is statistically significantly negatively associated only with WHODAS domain Life activities; Schizotypal, Borderline, Avoidant, and Dependent PDs are all statistically significantly positively associated with three domains of WHODAS: Cognition, Getting along and Participation, but Schizoid PD is positively associated with two of six WHODAS domains: Cognition and Getting along (see **Table 1**).

In **Table 2**, correlations between 34 PPTs and 6 WHODAS domains are presented. As it can be seen, 17 of 34 PTTs (Submissiveness, Intimacy avoidance, Restricted affectivity,

TABLE 1 | Spearman's rank correlation coefficients between personality disorders scales and six domains of functioning.

WHODAS 2.0.	Paranoid	Schizoid	Schizotypal	Antisocial	Borderline	Histrionic	Narcissistic	Avoidant	Dependent	Obsessive-Compulsive
Cognition	.10	.57**	.39*	.15	.49**	−.14	−.02	.65**	.50**	−.08
Mobility	.15	.14	.27	.21	.23	.04	.07	.16	.26	−.20
Self-care	.09	−.06	.16	.19	.20	.23	.14	.05	.20	−.23
Getting along	.11	.58**	.32*	.17	.41**	−.23	−.08	.62**	.38*	−.12
Life activities	−.08	−.01	.15	.19	.10	.13	−.06	.11	.22	−.39*
Participation	.22	.27	.40**	.27	.47**	.11	.12	.39**	.48**	−.13

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

Perfectionism, Callousness, Hostility, Manipulativeness, Will to power, Grandiosity, Histrionism, Attention seeking, Impulsivity, Recklessness, Eccentricity, Cognitive dysregulation, Suspiciousness, and Self-Harm) show no statistically significant correlation with any of WHODAS domain in the group of patients with AUD. WHODAS domain Cognition is positively associated with all four traits from Negative Emotionality domain (Emotional lability, Anxiousness, Depressivity, Distrustfulness), three of five traits from the Detachment domain (Social withdrawal, Social detachment, and Anhedonia), with Irresponsibility from Disinhibition domain and with Dissociation proneness from Psychoticism domain. WHODAS domain Mobility is positively associated with eight PPTs: Separation insecurity, Low self-esteem, Anxiousness, Depressivity, Irresponsibility, Unusual perceptions, Unusual beliefs, Dissociation proneness. Six PPTs (Anxiousness, Depressivity, Social withdrawal, Social detachment, and Anhedonia, Deceitfulness, Irresponsibility, Dissociation proneness) is significantly positively related to Getting along domain; two, Anxiousness (positively), Orderliness (negatively), to Life activities domain, and nine PPTs, Separation insecurity, Guilt/shame, Emotional lability, Anxiousness, Depressivity, Irresponsibility, Aggression, Unusual perceptions, and Dissociation proneness, to Participation domain. No statistically significant correlation was found with Self-care domain of WHODAS (see **Table 2**).

Taking into account the significant number of PDs scales and PPTs scales found to be associated with WHODAS domains, at the next stage of data analysis, series of stepwise regression analysis was conducted to find out which PDs and PPTs could be predictive for functioning impairment. In each regression, the WHODAS domains score was included as a dependent variable, and PDs and PPTs scales found to be statistically significantly associated with particular WHODAS domain (see **Table 3**), were entered as independent variables. Seven separate regression analyses were performed, first three analyses with PDs scales as independent variables, and then four analyses with PPTs scales as independent variables.

Cognition Domain

The results of the stepwise regression analyses indicated that PD Avoidant scale positively predicted impairment in the Cognition domain and explained 45% of the total variance. When PPTs were analyzed as independent variables, in step 1 of the model, the PPT Social Withdrawal explained 38% of the total variance in Cognition domain. In step 2, the PPT Social Withdrawal along with PPT Irresponsibility explained 53% of the total variance in Cognition domain, and in step 3, the PPT Social Withdrawal along with PPT Irresponsibility and PPT Guilt/Shame explained 61% of the total variance in Cognition domain (see **Table 3**).

Getting Along Domain

The results indicated that PD Avoidant scale positively predicted impairment in Getting Along domain and explained 47% of the total variance in this domain. When PPTs were analyzed as independent variables, in step 1 of the model, the PPT Social Withdrawal explained 37% of the total variance in Getting Along domain. In step 2, the PPT Social Withdrawal along with PPT Depressivity explained 48% of the total variance in Getting Along domain, and, in step 3, the PPT Social Withdrawal along with PPT Depressivity and PPT Irresponsibility explained 53% of the total variance in Getting Along domain (see **Table 3**).

Participation Domain

The results indicated that PD Dependent scale positively predicted impairment in Participation domain and explained 22% of the total variance in the domain. When PPTs were analyzed as independent variables, in step 1 of the model, the PPT Separation Insecurity positively predicted impairment in Participation domain and explained 25% of the total variance in the domain (see **Table 3**).

Life Activities Domain

Finally, it was found that PPT Orderliness negatively predicted impairment in the Life Activities domain and explained 14% of the total variance of this domain (see **Table 3**).

Based on performed Post Hoc power analysis for evaluation for 1) the deviation of R^2 from zero for total model and 2) the increase of R^2 in the multiple regression model, it was found that almost in all cases presented in **Table 3**, the power of the performed test was higher than 0.80, mostly power indices were from 0.95 to 0.99. Slightly lower than acceptable (0.80), it was for R^2 change for Orderliness in the last step of the model, when predicting Life Activities domain (power of that test was 0.78), and not acceptable (0.50) for R^2 change for Irresponsibility, when predicting Getting along domain.

DISCUSSION

To achieve the aim of this study, it was necessary to identify the extent to which LCPI v2.1. scales of PDs and PPTs predict impairments in functional domains in patient group with AUD.

TABLE 2 | Spearman's rank correlation coefficients between pathological personality traits and six domains of functioning.

Pathological personality traits	Domains of functioning						Pathological personality traits	Domains of functioning					
Subordination	**Cognition**	**Mobility**	**Self-care**	**Getting along**	**Life activities**	**Participation**	**Antagonism**	**Cognition**	**Mobility**	**Self-care**	**Getting along**	**Life activities**	**Participation**
Submissiveness	.24	.21	.21	.23	.11	.24	Callousness	.16	.20	.17	.14	.14	.26
Separation insecurity	.22	.36*	.21	.13	.30	.29*	Hostility	.18	.19	.07	.21	.07	.24
Low self-esteem	.16	.29*	.20	.13	–.04	.12	Manipulativeness	.06	.17	.25	–.00	.17	.18
Guilt/shame	.30*	.11	.16	.25	.28	.33*	Will to power	–.00	.13	.19	–.00	.13	.13
							Grandiosity	–.10	.11	.14	–.10	–.09	.07
							Histrionism	.15	–.00	.00	.05	.05	.09
							Attention seeking	.02	.06	.18	–.11	.08	.16
							Deceitfulness	.11	.02	.14	.30*	–.02	.06
Negative Emotionality							**Disinhibition**						
Emotional lability	.39**	.19	.12	.24	.15	.47**	Impulsivity	.15	–.04	–.01	.12	.12	.24
Anxiousness	.43**	.29*	.25	.31*	.32*	.46**	Recklessness	–.04	.05	.01	–.01	–.03	.05
Depressivity	.45**	.29*	.28	.44**	.06	.42**	Irresponsibility	.54**	.29*	.28	.46**	.28	.39**
Distrustfulness	.29*	.07	.04	.22	–.15	.26	Aggression	.20	.17	.18	.15	.08	.30*
Detachment							**Psychoticism**						
Social withdrawal	.56**	.10	–.15	.55**	–.01	.20	Eccentricity	.24	.21	.21	.23	.11	.24
Social detachment	.49**	.13	–.05	.55**	.02	.23	Unusual perceptions	.22	.36*	.21	.13	.30	.29*
Anhedonia	.40**	.14	–.08	.36*	–.02	.20	Unusual beliefs	.16	.29*	.20	.13	–.04	.12
Intimacy avoidance	.18	.10	.14	.16	–.12	.17	Cognitive dysregulation	.20	.11	.18	.09	–.10	.17
Restricted affectivity	–.00	.22	–.06	–.01	.01	–.12	Dissociation proneness	.59**	.37**	.17	.46**	.31	.44**
							Suspiciousness	.04	.15	.13	.02	–.02	.22
							Self-Harm	.08	.22	.10	–.01	–.01	.25
Compulsivity													
Perfectionism	.04	–.06	–.18	.02	–.27	–.07							
Orderliness	–.16	–.13	–.19	–.22	–.40**	–.15							

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

TABLE 3 | Stepwise regression analysis for six domains of functioning as the dependent variables and personality disorders scales (PDs) and pathological personality traits (PPTs) scales as independent variables in group of patients with AUD.

	β	F	R^2	ΔR^2 (Adjusted R^2)		β	F	R^2	ΔR^2 (Adjusted R^2)
Cognition (DV*)					**Cognition** (DV*)				
Step 1		37.89**	.45	.45 (.44)	Step 1		27.91**	.38	.38 (.37)
PD Avoidant	.67**				PPT Social withdrawal	.62**			
					Step 2		24.92**	.53	.14 (.51)
					PPT Social withdrawal	.49**			
					PPT Irresponsibility	.40**			
					Step 2		22.82**	.61	.08 (.58)
					PPT Social withdrawal	.52**			
					PPT Irresponsibility	.34**			
					PPT Guilt/shame	.29*			
Getting along (DV*)					**Getting along** (DV*)				
Step 1		42.23**	.47	.47 (.46)	Step 1		27.17**	.37	.37 (.36)
PD Avoidant	.69**				PPT Social withdrawal	.61**			
					Step 2		20.50**	.48	.10 (.46)
					PPT Social withdrawal	.50**			
					PPT Depressivity	.34*			
					Step 3		16.08**	.53	.04 (.49)
					PPT Social withdrawal	.46*			
					PPT Depressivity	.25*			
					PPT Irresponsibility	.24*			
					Life activities (DV*)				
					Step 1		5.95*	.14	.14 (.11)
					PPT Orderliness	−.37*			
Participation (DV*)					**Participation** (DV*)				
Step 1		12.93**	.22	.22 (.20)	Step 1		15.33**	.25	.25 (.24)
PD Dependent	.47**				PPT Separation insecurity	.50**			

*$p < 0.05$. **$p < 0.01$. DV*, dependent variable.*

Results of the study show that Avoidant PD scale positively predicts impairments in the Cognition domain (R^2 = .45) and Getting along domain (R^2 = .47) in patients with AUD. This means that from AUD patients who have a high manifested pattern of Avoidant personality, one can expect that they will have impairments in such cognitive functions as concentrating, remembering, problem-solving, learning and communicating, and difficulties with interactions with other people.

Analyzing what PPTs, relevant to Avoidant PD, are predictive to these two functional domains, it was found that: 1) three PPTs: Social Withdrawal (ΔR^2 =.38) [which, according to DSM-5, is defined as "preference for being alone to being with others, reticence in social situations, avoidance of social contacts and activity and lack of initiation of social contact" [(5), p. 831)], Irresponsibility (ΔR^2 =.14) [which is characterized as "disregard for and failure to honour financial and other obligations or commitments, lack of respect for and lack of follow-through on agreements and promises" [(5), p. 765)], and Guilt/Shame (ΔR^2 =.08) positively predicted functional difficulties in the Cognition domain; the effect size when all three variables were included in the model, was R^2 = .61, which is characterized as large effect (based on Cohen (38), R^2 = 0.015 denotes a small effect, R^2 = 0.125 a medium effect and R^2 = 0.255 a large effect); 2) Social Withdrawal (ΔR^2 = .37), Depressivity (ΔR^2 = .10), and Irresponsibility (ΔR^2 = .04) most accurately and consistently predict functional difficulties in Getting along domain (but it must be mentioned that in this model, the personality trait Irresponsibility does not have sufficient strength for further interpretation). These findings imply that for AUD patients who have a highly manifested pattern of social withdrawal, feelings of inadequacy, and hypersensitivity to negative evaluation, it is possible to predict functional difficulties in Cognition domain, but for patients with highly manifested pattern of social withdrawal in combination with Depressivity, which is characterized as feelings of being down, hopeless, and pessimism about the future [(5), p. 779], it is possible to predict difficulties in understanding, communicating and interacting with other people.

Knowing which PPTs are predictive for impairment in Cognition domain and Getting along domain, specialists can provide more individual approach in treatment of patients with AUD. For example, they can anticipate that patients with high scores of social withdrawal may be "bad" candidates for various types of treatment that will require group work. Specialists treating such patients, especially in psychoeducational programs, must take into account that for such an individual it could be difficult not only to take part in the group work, but also to understand, analyze, and remember discussed material. So, when working with such patients, it could be useful to use methods that reduce intolerable feelings, especially in the initial stages of treatment, when the highest rates of dropouts mostly occur.

It has been also found that PD that most likely predicts difficulties in Participation domain is Dependent PD scale (R^2 = .22) that corresponded to medium effect size. The possibility to analyse the results in greater detail allows to find out that the

most significant predictor of difficulties in Participation domain is PPT Separation insecurity (R^2 = .25), which is related to "fears of rejection by and/or separation from significant others, associated with fears of excessive dependency and complete loss of autonomy" [(5), p. 767] and is one of the most relevant traits of Dependent PD. It means that AUD patients who have a high manifested pattern of submissive and clinging behavior related to an excessive need to be taken care of, tend to have functional difficulties in Participation domain that include community activities. So it could be suggested that, when working with individuals who have pronounced personality trait Separation insecurity, the specialist must take into account that the individual will have difficulties with participation and co-responsibility, and the dependent individual will expect instructions, advice, and will expect the specialist to act authoritatively, on the directive way. Such patients often indulge in a specialist and follow his/her instructions not because the individual believes in those instructions and not for the sake of improvement, but so that the specialist would not leave them. They are often afraid of improvement, because then they will have to stop treatment, and thus the relationship with the specialist.

Finally, it was found that PDs do not predict domain of Live activities, but, looking at the obtained results on the traits level, it was found that PPT Orderliness negatively predict functional difficulties in this domain (R^2 = .14). This means that for AUD patients who have a high manifested Orderliness, which is related to preoccupation with details, organization, and order, it is possible to predict that functional difficulties will be somewhat smaller in Live activities domain that includes difficulty with day-to-day activities (i.e., the ones people do on most days, including those associated with domestic responsibilities, leisure, work, and school).

Generally, the results are consistent with results of previous studies and more precisely explain the problems of functioning of the patients of the AUD group in terms of both PDs and PPTs. For example, it was shown (30) that people with dual diagnoses have difficulty developing a meaningful social life and have anhedonia and anxiety.

Both alcohol abuse and PDs are difficult to treat and are a challenge for healthcare providers. PDs cause difficulties in developing therapeutic relationships, difficulty in attending, and more frequent relapses (drop-outs). Moreover, based on results of this study, it can be concluded that assessment of PPTs could constitute an important target of relapse prevention and treatment programmes in patients' group with AUDs, as evidenced by medium to large effect sizes (R^2 ranging from 0.14 to 0.61).

AUD persons may have problems with the self-care and mobility functioning, but, in this study, it was not revealed that there would be a relation between self-care and mobility and PDs or PPTs, which was discovered in other studies for patients with AUD. These results are partially consistent with those reported by Keeley et al. (39) with a clinical sample. Researchers found the facets to be most closely related to the domains of understanding and communicating, getting along with people, and participation in society. Similarly, in the present sample of AUD patients, we found that the personality traits are related mainly to aspects of the interpersonal relationships of these patients, which constitutes validity evidence consistent with that shown by other authors.

To summarize, it is important to pay attention that in the practice of individual analysis of patient traits, PPTs can form a unique profile and combine a number of variations, which indicates that, when analyzing the types of PDs based on a categorical approach, it is risky to ignore the unique PPTs of patient profile, as this may cause errors in treatment planning and forecast.

Limitations

It is known that cross-sectional studies have limitations to predictions. For example, the results could differ in another time period; therefore, it would be necessary to conduct a longitudinal study. It must be acknowledged that there is disadvantage in the fact that the study included only patients who had turned to a specialist for help and did not include those who had turned to a specialist or visited private medical institutions. Another important factor is the duration of the individual's illness with the AUD, which was not controlled in this study, but as it is known, has a negative impact on the various areas of functioning (40). Studies often show a high percentage of PDs in the group of patients with substance use disorder, and B-cluster PDs are more common (3, 18, 19, 41), but there were no patients with PD diagnosis in this sample, which most likely reflects the limitation of the patient selection procedure on the one hand, since inclusion in the sample served as an AUD diagnosis criterion and patients with comorbid Axis I disorders were not included, which could potentially conceal a large population of patients with PDs as well. Moreover, it is necessary to note some difficulties in the diagnosis of comorbid disorders. It is possible that inclusion of all patients with comorbid mental disorders and mandatory additional diagnostics of the mental status of patients, as well as more sufficient statistical analysis with control of confounded variables can provide more clear and reliable results.

There were some more limitations regarding the sample size and composition. First, it represents only Latvian speaking part of AUD patients, second, sample size is small, which limits the possibility to generalize findings of the study. Increasing of the sample size might have improved the estimated reliability of the scores by increasing their variability (42) and the power of the statistical methods employed. Despite this limitation, authors of this study believe that their sample size was sufficient for successful implementation of the conducted statistical analyses, which was approved by the results of the Power analysis.

Due to the small sample size, the gender factor was not taken into account in this study, although it was shown that there are gender differences in personality traits, for example, obsessive-compulsive, hysterical, and antisocial PDs prevail among women (43).

Also, the limitations concern the possibility that functioning might not be adequately assessed in this type of patients when

using self-report as the test measure. Optimal use of multisource data, such as family members' reports or register data, could improve the prediction of behavior in the clinical assessment of psychopathology (30, 44).

CONCLUSIONS

This study revealed that the obtained results add deeper insight into understanding of the relationship between PDs scales, PPTs, and functioning domains in patients with AUD. The avoidant and dependent PDs scales predict impairment in functioning domains in AUD patients but, on the PPT level, there was found additional useful information. Social withdrawal, Irresponsibility, Guilt/Shame, Separation insecurity, and Depressivity predict impairment in everyday functioning. These results suggest that not only PDs scales but also evaluation of PPTs should be taken into consideration by practitioners for planning more effective approaches in treatment of alcohol addicted patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All patients provided their written informed consent to participate in this study. The study was reviewed and approved by the Rīga Stradiņš University Research Ethics Committee and by the Riga Psychiatry and Narcology Centre.

AUTHOR CONTRIBUTIONS

JK, VP, VS, KM, and AS have contributed to the conception and design of the study "Relationship between personality disorders scales, pathological personality traits and six domains of functioning in sample with alcohol use disorder". JK and VS organized the database. JK and VP performed the statistical analysis. JK wrote the first draft of the manuscript. JK and VS wrote sections of the manuscript. All authors contributed to the manuscript revision and have approved the submitted version.

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BRIEF RESEARCH REPORT
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Traumatic Events and Substance Use Disorders in Adolescents

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Objectives: Adolescents with substance use disorders (SUD) frequently report traumatic events (TEs) and symptoms of post-traumatic stress disorder (PTSD). This study aimed to assess whether lifetime prevalence rates of TEs and PTSD are related to SUD severity in adolescent psychiatric patients.

Methods: We analyzed *N* = 114 self-reports of treatment-seeking German adolescents aged 12 to 18 years, who visited a specialized SUD outpatient unit. Standardized questionnaires were applied to assess SUD severity, the number of TEs and DSM-IV PTSD criteria.

Results: Patients fulfilling PTSD criteria (28% of the total sample) had a higher Drug Use Disorders Identification Test (DUDIT) score compared to non-PTSD patients with TEs (p <.001), and compared to adolescents without TEs or PTSD (p = .003). Additionally, SUD severity was positively associated with the number of TEs and the number of intrusion, hyperarousal, and avoidance symptoms (all r = .33 to.48, all p <.01).

Discussion: Adolescent patients with SUD reported 3-times higher rates of TEs, and a 5-time higher prevalence of PTSD following TEs, than the general adolescent population. Adolescent SUD patients with PTSD reported more severe substance use problems than patients without PTSD—regardless of previous TEs. Longitudinal studies are needed in order to investigate the temporal relationship between TEs, PTSD and SUD.

Keywords: teenager, trauma, addiction, self-medication, traumatic experiences

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INTRODUCTION

Adolescence, as defined by the World Health Organization, is a phase of life between ages 10 and 19 that marks the transition from childhood to adulthood (1, 2). Adolescents are "biologically wired" (3) to engage in risky and potentially harmful behavior including the use of psychoactive substances, which might lead to the development of a substance use disorder (SUD) (4). Moreover, the increase in risk behavior might lead to identification with substance-related subcultures (e.g. "psychonauts"), in which use of novel psychoactive substances (NPS) is widespread (5). In Germany, the lifetime prevalence rate of SUD in adolescents and young adults is 28.6% (6), with SUD being associated with worse performance in school, worse overall health, higher mortality rates and increased rates of comorbid psychiatric disorders such as post-traumatic stress disorder (PTSD) (7–9).

PTSD is an anxiety disorder that may develop subsequent to exposure to traumatic events (TEs), either experienced or witnessed. TEs are defined as experiences that involve actual or threatened

death, serious injury, or threat to the physical integrity of oneself or others, and are responded to with intense fear, helplessness or horror (10). PTSD diagnosis requires an experience of a TE (Criterion A) that is followed by three major symptom clusters: intrusive recollections of the event (Criterion B), avoidance of event-related stimuli, or emotional numbing (Criterion C) and hyperarousal (Criterion D).

Common developmental pathways for SUD and PTSD have been proposed, given the high rates of co-occurrence between the two disorders (11): Firstly, there is evidence from studies in adult patients that SUD and PTSD have common genetic and family environmental risk factors (12). Secondly, substance use in general is related to more frequent risk behavior (13), which increases the likelihood of experiencing TEs, and therefore developing PTSD (14, 15). For example, patients with a SUD are more likely to engage in other-directed than self-directed violence, increasing the risk of encountering TEs (16). Finally, the self-medication hypothesis derives from clinical observations that the specific actions or effects of each class of drugs relieve or change a range of painful affect states in patients with PTSD (11, 17, 18).

Notably, the rate at which people are exposed to TEs peaks during adolescence (19) and this increased exposure is naturally associated with a higher rate of PTSD (14). In sum, adolescents typically engage in high-risk behavior thus increasing their risk for both substance use and TEs, which might lead to subsequent disorders, e.g. SUD and/or PTSD. There is a growing epidemiological and clinical literature documenting the frequent co-occurrence of SUD and PTSD in adolescents (20). Several studies indicate that between 20 and 54% of North American adolescents with SUD also have co-occurring PTSD (21, 22). In German adolescents, SUD occurs at a rate of 30% in patients who fulfill PTSD criteria (23). Moreover, the severity of substance use (except for alcohol use) correlates positively with the number of PTSD symptoms in adolescents (24).

Previous research established the link between SUD and PTSD (11, 18, 20, 24). However, it remains to be explored if SUD severity is only increased in adolescents with co-occurring PTSD, or linked to the occurrence of TEs in general, providing an insight into the pathomechanisms of both disorders.

Here, we assess the prevalence of both lifetime TEs and PTSD according to DSM-IV criteria among German adolescents seeking treatment for a SUD and compare these prevalence rates with the general adolescent population. We compare three groups of SUD treatment-seeking adolescents: adolescents fulfilling DSM-IV PTSD diagnostic criteria ('PTSD' group), adolescents with a history of TEs but no PTSD ('TE' group) and adolescents with no TEs and no PTSD ('NoTE' group).

We hypothesize that (1) adolescents with a SUD present with higher rates of current PTSD and past TEs than the general adolescent population. We predict that (2) SUD severity will be higher in the PTSD and TE group than in the NoTE group and that (3) SUD severity is positively associated with the number of PTSD symptoms present in each symptom cluster.

METHOD

Participants

Between November 2017 and October 2019, n = 178 treatment-seeking adolescents at an outpatient clinic for adolescent substance abuse participated in the study. N = 64 adolescents (36%) did not complete all necessary questionnaires and were therefore excluded. In the final sample of n = 114 patients, the mean age was 15.8 years (SD = 1.3) with 43% (n = 49) females, see **Table 1**. Secondary education levels were predominantly classified as low level (55%), while household income was predominantly classified as medium level (57%), see **Table 1**.

Procedures

Data collection was embedded into the standard diagnostic procedures at the outpatient clinic. Questionnaires were handed out to the patients and their legal guardians at the first consultation appointment in the outpatient department. The criteria for harmful use and dependence for all relevant psychoactive substances according to the ICD-10 guidelines (25), were assessed in a personal interview by a trained clinical psychologist. Study assessments took place before any intervention started. The study was conducted in accordance with the Declaration of Helsinki. Patients as well as legal guardians were informed about the projects thoroughly and comprehensively. Written informed consent was obtained from all legal guardians. All procedures of this study were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018) and registered at clinicaltrials.gov (NCT03444974). No reimbursement was offered to patients.

Measures

Traumatic Experiences, PTSD Symptoms and PTSD Diagnosis

The University of California at Los Angeles Post Traumatic Stress Disorder Reaction Index for DSM-IV (UCLA PTSD (26) is a self-report instrument that screens for exposure to TEs, and assesses PTSD symptoms in school-age children and adolescents. It has been translated for, and used with German-speaking populations (27). The instrument consists of a trauma history section, in which patients indicate the TE that afflicts them the most and the traumatizing features of the event (Criterion A). The next section assesses the frequency of occurrence of PTSD symptoms during the past month (rated from 0 = none of the time to 4 = most of the time). The items map directly onto DSM-IV intrusion/re-experience (Criterion B), avoidance (Criterion C), and hyperarousal (Criterion D) criteria. Scoring algorithms permit tabulation of UCLA PTSD total score, and A, B, C, and D subscale scores. The DSM-IV diagnosis PTSD is given when all four criteria (Criterion A, B, C, and D) are present (26). In the current sample, internal consistency was good for criterion A and B (α = .83 and.86, respectively), and acceptable for criterion C and D (α = .73 and.75, respectively).

TABLE 1 | Sociodemographic characteristics of the complete sample, and the three subgroups.

Demographics	*Total (n = 114)*	*Analysis group*			Group comparison		
		NoTE (n = 35)	*TE (n = 47)*	*PTSD (n = 32)*	Test statistic (*df*)	p	*Effect size*
Mean age (*SD*)	15.8 (1.3)	15.5 (1.3)	16.0 (1.3)	15.8 (1.2)	F (*113*) = 1.32	.271	η_p^2 = .023
Gender:					χ^2 (*2*) = 2.427	.297	ϕ = .15
Female (%)	49 (43)	12 (34)	27 (57)	17 (53)			
Male (%)	65 (57)	23 (66)	20 (43)	15 (47)			
Household income: # of patients in category (%), missing *n* = 60	(*n* = 54)	(*n* = 22)	(*n* = 21)	(*n* = 11)	χ^2 (*4*) = 1.525	.822	.17
Low income	9 (17)	4 (18)	4 (19)	1 (9)			
Middle income	31 (57)	11 (50)	13 (62)	7 (63)			
High income	14 (26)	7 (32)	4 (19)	3 (25)7			
Educational level: # of patients in category (%), missing *n* = 38	(*n* = 76)	(*n* = 22)	(*n* = 34)	(*n* = 20)	χ^2 (*6*) = 4.773	.573	.25
Low	37(55)	9 (41)	16 (47)	12 (60)			
Middle	20 (26)	6 (27)	11 (32)	3 (15)			
High	8 (11)	4 (18)	3 (9)	1 (5)			
Other	11 (14)	3 (14)	4 (12)	4 (20)			
Substance abuse: # of patients presenting with harmful use or dependence per substance (%), missing *n* = 2	(*n* = 112)	(*n* = 35)	(*n* = 47)	(*n* = 30)			
Alcohol	44 (39)	12 (34)	23 (49)	9 (30)	χ^2 (*2*) = 3.286	.193	.17
Cannabis	89 (80)	29 (83)	38 (81)	22 (73)	χ^2 (*2*) = 0.993	.609	.09
Stimulants (amphetamine, methamphetamine, or MDMA)	49 (44)	13 (37)	18 (38)	18 (60)	χ^2 (*2*) = 4.408	.110	.20

PTSD, Post-traumatic stress disorder according to DSM-IV; TE, Traumatic event; MDMA, methylenedioxymethamphetamine. A clinical psychologist performed the diagnosis of harmful use or dependence syndrome, and multiple diagnoses per patient were possible. For the differences in substance abuse, the p-value was adjusted according to the Bonferroni-procedure to p < .02.

Substance Use and SUD Severity

The Drug Use Disorders Identification Test [DUDIT; (28)] is a self-report instrument composed of 11 items identifying problems related to substance use. Scoring of the DUDIT is two-fold: items 1 to 9 are scored on a five-point Likert scale, while items 10 and 11 are scored on a three-point scale. The overall score is calculated by summing the scores on all items, with a maximum score of 44. In the current sample, internal consistency of the DUDIT was good with α = .87.

SUD Diagnosis

A clinical psychologist assessed criteria for harmful use and dependence syndrome for all relevant psychoactive substances according to ICD-10 (24) in a personal interview with the patients. The SUD diagnosis was established in a consensus-based procedure by interviewing psychologist and a board-certified child and adolescent psychiatrist

Sociodemographic Background

Thirty-six generic questions were presented to the parents. We analyzed the questions indicating age in years, gender, and education level (low, medium, high) of the patient as well as yearly household income (low, medium, high). Adolescents' educational levels and parental income levels were assessed according to previously established criteria (29).

Analyses

All analyses were conducted with IBM SPSS Statistics 25.0. Based on UCLA PTSD results, patients were separated into three analysis groups: PTSD diagnosis ('PTSD' group), TE but no PTSD diagnosis ('TE' group), no TE and no PTSD diagnosis ('NoTE' group). To investigate the relationship between SUD and PTSD symptoms, Pearson's correlation coefficient r was calculated between DUDIT score, the number of possible TEs, and the number of PTSD symptoms within each criterion cluster (Clusters A, B, C, and D). An analysis of variance (ANOVA) was performed to test for mean differences in DUDIT score between the three groups. To determine if the ANOVA is an appropriate procedure we checked the normality of the dependent variable (DUDIT score) by means of the Shapiro–Wilk test (30). Additionally, to check for homogeneity of variances, Levene's test was conducted. DUDIT score was normally distributed in the NoTE group (W = .944; p = .072), the TE group (W = .956; p = .075), and the PTSD group (W = .952; p = .16). Further, Levene's test showed that the variance of DUDIT score was equal across groups, F (2, 111) = 0.8, p = .452. In cases were the F-test across groups was significant, post-hoc multiple comparisons using the Bonferroni correction were conducted to identify groups differing from each other regarding their mean DUDIT score. To detect demographic differences between the groups, χ^2-tests were conducted. Level of significance was defined as p <.05

(two-tailed). Since patients could present with harmful use or dependence for multiple substances, multiple univariate χ^2-tests were used to assess group differences in this variable. For this specific analysis, the level of significance was adapted according to the Bonferroni-procedure to $p < .05/3$. Effect sizes were classified according to Cohen (31) into small effects ($|r| \geq .10$, partial eta-square $\eta_p^2 \geq .01$), medium effects ($|r| \geq .30$, $\eta_p^2 \geq .06$), and large effects ($|r| \geq .50$, $\eta_p^2 \geq .14$).

RESULTS

Sociodemographic Characteristics and Substance Abuse

The majority of patients reported enough symptoms to qualify for cannabis abuse (80%), followed by alcohol abuse (39%) and stimulant (amphetamine, methamphetamine, or MDMA) abuse (44%), see **Table 1**. None of the patients reported use of NPS during the past 12 months. The three groups (PTSD, TE, and NoTE) did not differ in any of the assessed sociodemographic characteristics nor in their SUD diagnoses, see **Table 1**.

Prevalence Estimates

The majority of patients (69%) reported at least one lifetime TE. **Figure 1** illustrates that "non-domestic violence" followed by "sexual abuse" were the most-prevalent TEs categories, whereas "war" and "medical treatment" represented the least-frequent categories. Over one third of the patients with TE (41%) also fulfilled the DSM-IV diagnostic criteria for a PTSD according to the UCLA PTSD scale, resulting in a point prevalence of 28% for PTSD in the total sample.

The Relationship Between TEs, PTSD Symptoms and SUD Severity

The number of symptoms in each PTSD symptom cluster (A = number of traumatizing features of TEs, B = intrusion, C = avoidance, D = hyperarousal) correlated positively with each other (all $r = .23$ to $.56$, all $p < .038$) and with DUDIT score (all $r = .33$ to $.48$, all $p < .003$) with an exception of DUDIT score and Cluster A ($r = .20$, $p = .08$). The correlations of DUDIT score and clusters B, C, and D can be classified as medium size effects ($r = .30$ to $.49$), see **Table 2**.

Group Differences in SUD Severity

The three patient groups (PTSD, TE, NoTE) differed in their mean DUDIT score, $F(2, 111) = 7.86$, $p = .001$, $\eta_p^2 = .124$. Post-hoc multiple comparisons revealed that the PTSD group scored a significantly higher mean DUDIT score when compared to the TE group ($t(77) = 3.812$, $p = .0008$), and to the NoTE group ($t(65) = 3.33$, $p = .003$). No difference was found between the TE and the NoTE group ($t(80) = .039$, $p = .969$), see **Figure 2**.

DISCUSSION

We investigated differences in SUD severity between three groups (PTSD, TE, NoTE) of treatment-seeking adolescents at a German outpatient clinic for adolescent substance abuse. Additionally, we assessed the past-month-prevalence of PTSD and lifetime-prevalence of TE. In accordance with our hypothesis as well as earlier studies, our results indicate that adolescents with SUD were more likely to report TEs [69% vs. 21% (32)], more likely to suffer from PTSD following TEs [41% vs. 8% (33)], and more likely to fulfill the diagnostic criteria for PTSD compared to the general adolescent population [28% vs. 2% (32)]. Contrary to our hypothesis, only the PTSD group displayed more severe SUD symptoms than the TE group and the NoTE group. Additionally, we confirmed the hypothesis that SUD severity is positively associated with the number of hyperarousal, intrusion, and avoidance symptoms.

We were not able to delineate the reason for the positive relationship between the number of PTSD symptoms and SUD severity. Patients with stronger PTSD symptoms might self-medicate more heavily with psychotropic substances, and

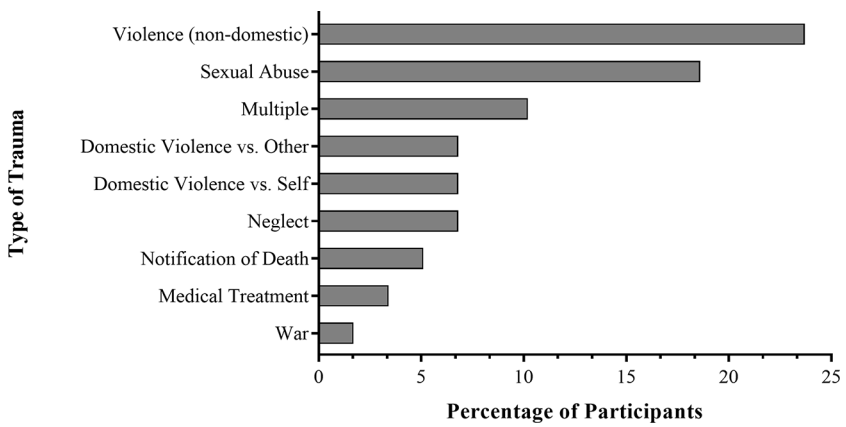

FIGURE 1 | The percentage of patients ($n = 59$) that described a particular type of event as their most traumatizing experience. Total $n = 114$, with $n = 35$ reporting no traumatic experiences, and $n = 20$ not clearly identifying the most traumatizing experience.

TABLE 2 | Bivariate Pearson correlation coefficients between DUDIT score, the number of Traumatic events (TE), and the number of symptoms present in Clusters A, B, C, and D of the UCLA PTSD Questionnaire.

	DUDIT score	Number of TE	Sum Cluster A	Sum Cluster B	Sum Cluster C	Sum Cluster D
DUDIT score	–	.21*	.20	.33**	.35**	.48**
Number of TE	.21*	–	.13	.34**	.27*	.16
Sum Cluster A	.20	.13	–	.45**	.27*	.23*
Sum Cluster B	.33**	.34**	.45**	–	.56**	.54**
Sum Cluster C	.35**	.27*	.27*	.56**	–	.47**
Sum Cluster D	.48**	.16	.23*	.54**	.47**	–

*DUDIT, Drug use disorders identification test; PTSD, Post-traumatic stress disorder according to DSM-IV. Cluster A = Traumatizing qualities of event. Cluster B = Intrusion. Cluster C = Avoidance. Cluster D = Hyperarousal. SUD, substance use disorder according to ICD-10, including substance abuse and substance dependence; TE, Traumatic event. *p < 0.05, **p < 0.01.The number of cases per cell varied due to presence of a PTSD between n = 79 and 114.*

therefore develop more SUD symptoms (11, 17, 18). Alternatively, when functional substance use develops into a SUD, PTSD symptoms might increase as a results of reduced overall mental health (34). Additionally, the development of SUD-related withdrawal symptoms, such as anxiety or depression, might lead to stronger PTSD symptoms (34). Consequently, self-medication of PTSD symptoms with psychotropic substances should be seen as a risk factor, not only for a subsequent SUD, but also for an increase of PTSD symptoms later on. It remains to be explored, if patients with more severe PTSD engage in more substance use, if patients with heavier substance use are more vulnerable to develop PTSD following TEs, or whether a more complex bidirectional relationship exists. To assess these complex relationships, longitudinal studies are needed that frequently assess occurrence of TEs, PTSD symptoms, substance use, and SUD symptoms.

Our finding that TEs alone are not associated with higher SUD severity is supported by research examining the relationship between PTSD and SUD in adolescents and adults (35–36). Reed et al. (37) found that in adolescents, the presence of PTSD but not TEs without PTSD is associated with a higher risk for future substance abuse or dependence. Furthermore, Driessen et al. (35) observed that a PTSD diagnosis but not the number of TEs correlates with SUD severity. Finally, Kok et al. (36) reported, that trauma-related variables do not add information about variation in drug use severity compared to PTSD symptoms. This line of research indicates that TEs are unrelated to SUD severity and the development of SUD symptoms.

Previous studies with adult SUD patients reported similar results to ours, insofar as all three symptom clusters correlated positively with SUD severity (36, 38). However, research in adolescents indicated only avoidance symptoms being positively associated with SUD severity, whereas hyperarousal symptoms were negatively correlated with SUD severity, and intrusion symptoms were not related to SUD severity at all (24). These conflicting results might be explained by the difference in sample selection. Specifically, we included patients with a SUD regardless of substance, whereas Donbaek et al. (24) excluded patients with an alcohol use disorder (AUD). Thus, the substance of use could be relevant for the relationship between SUD and PTSD symptoms. Indeed, a relationship between the use of specific substances and PTSD symptoms has been observed to exist in adults and adolescents. Explicitly it has been reported that the number of avoidance symptoms is higher in people who use alcohol (11, 38), sedatives, gamma-Hydroxybutyric acid (GHB), opioids (39), and heroin specifically (40). Moreover, people with an alcohol (38) or opioid (39) use disorder present with more hyperarousal symptoms than people who do not.

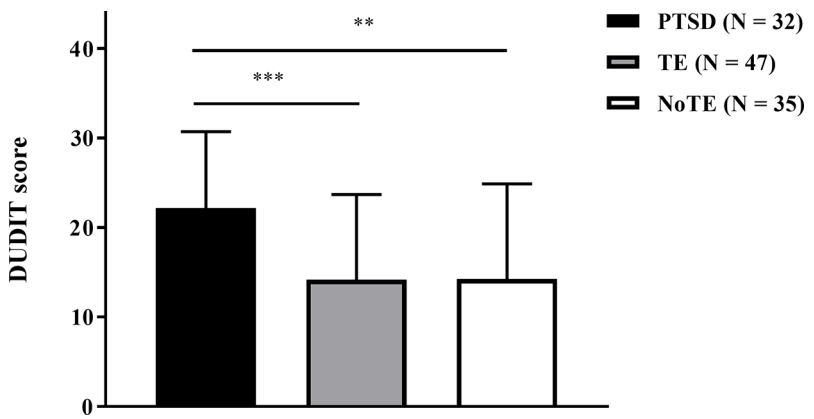

FIGURE 2 | The mean DUDIT score for the PTSD group (*n* = 32), the TE group (*n* = 47), and the NoTE group (*n* = 35). Mean differences were calculated through post-hoc multiple comparisons using the Bonferroni correction (**$p < 0.01$, ***$p < 0.001$).

Finally, Khoury et al. (38) and Avant et al. (39) report that the use of cannabis, cocaine, sedatives, and GHB is also related to more intrusion symptoms. While the use of specific substances does not seem to be related to specific symptom clusters, recent findings (11, 24, 38–40) confirm our results, that a higher level of substance use across substances is generally related to a higher number of PTSD symptoms across clusters.

Limitations

Our sample was limited to treatment-seeking adolescents with a SUD. Therefore, future research could investigate whether the presence of TE or PTSD influences the intensity of recreational substance use as well or if this influence is limited to SUD severity.

Our assessment of TEs and PTSD was based on self-report measures, which might be biased in the sense that patients might not recall all of their TEs. Additionally, all self-report instruments potentially suffer from response bias. Examples include misunderstanding of the items or a social-desirability bias (41). Furthermore, self-reports seem to underestimate trauma-specific cognitions, like intrusion symptoms (42). In future research it might be useful to use additional instruments such as standardized interviews to gain a more accurate picture of the PTSD symptoms clusters and number of TEs.

Furthermore, because we did not collect detailed data on substance use, we could not investigate the relationship between the use of specific substances and the number of PTSD symptoms in each cluster. Additionally, we took no measures to verify self-reports of substance use *via* biological measures. Therefore, even though none of the patients reported use of NPS, they might have unwillingly ingested them instead of a substance they were sold (e.g. NPS in an ecstasy pill).

Finally, our cross-sectional study lacks a possibility to investigate the question of timing and causality concerning PTSD and SUD development. A prospective longitudinal study design is necessary in order to answer the question, which symptoms or disorders develop first, and if TEs precede substance use or vice versa. This line of research would help to clarify the hypotheses concerning the relationship between the two disorders. For example, the finding that substance use and SUD symptoms generally appear after a TE would support the self-medication hypothesis.

Conclusion

Adolescents with SUD reported 3-time higher rates of TEs, and a 5-time higher prevalence of PTSD following TEs, than the general adolescent population. SUD was more severe in adolescents with PTSD than in adolescents without TEs or with TE anamnesis but no PTSD symptoms. Finally, the level of SUD severity was positively correlated with the number of PTSD-related intrusion, avoidance, and hyperarousal symptoms.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the University Hospital C. G. Carus, Dresden (EK 66022018). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LB analyzed the data and wrote the manuscript. SK-P participated in writing the manuscript and data analysis, and contributed to the discussion. VR participated in writing the manuscript and contributed to discussion. YG designed the study, participated in writing the manuscript, and contributed to discussion.

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Opioid Addiction/Pregnancy and Neonatal Abstinence Syndrome (NAS): A Preliminary Open-Label Study of Buprenorphine Maintenance and Drug Use Targeted Psychotherapy (DUST) on Cessation of Addictive Drug Use

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Background: Neonatal abstinence syndrome (NAS) is common, expensive, and hurts opioid addicted women and their families. Current treatments do not sufficiently address comorbid addictions, especially tobacco use, among pregnant buprenorphine-maintained women.

Methods: 25 consecutive admissions of pregnant, opioid addicted women were treated with buprenorphine maintenance and a novel intervention for pregnant opioid addicted patients, Drug Use Targeted Therapy (DUST). DUST entails a combination of informing women about the impact of various drugs on their fetus, discussing the woman's thinking about these consequences of drug use, and varying the frequency of psychotherapy; increasing if addictive drugs are used and decreasing if the woman wishes when drug use is stopped.

Results: 20/25 remained in treatment until delivery. All 20 women were using addictive drugs at admission. None were planned pregnancies. There was a high prevalence of emotional, physical or sexual abuse, criminal behavior, comorbid psychiatric disorders, and chronic pain. Nineteen stopped all addictive drugs. NAS was present for 5 out of 19 newborns with a duration of hospitalization from 4 to 6 days.

Conclusions: This preliminary open-label case series found that pregnant buprenorphine maintained women can stop tobacco. What has sometimes been termed "neonatal opioid abstinence syndrome" may most accurately be termed, "neonatal opioid/tobacco abstinence syndrome." If the treatment effectively addresses tobacco use, other addictive drugs are rarely used. DUST resulted in a 95% quit rate for addictive drugs.

Pilot data on this new intervention is limited; a case series that does not have a corresponding control group.

Keywords: neonatal abstinence syndrome, neonatal opioid abstinence syndrome, tobacco and pregnancy, buprenorphine and pregnancy, cold pressor test

INTRODUCTION

Neonatal abstinence syndrome (NAS) is the result of the sudden discontinuation of substances used by the mother during pregnancy. Since 2016, it has also been called, "Neonatal opioid withdrawal syndrome."(1) The incidence of NAS has quadrupled in 10 years to 6.5 per 1,000 live births and the cost of care has increased by six times in that period to $563 million, based on 2014 statistics (2). NAS causes suffering for neonates. Families must cope with witnessing a multitude of symptoms in the infant, including vomiting, diarrhea, decreased appetite, respiratory dysfunction, nasal congestion, frequent sneezing, crying, tremors, diaphoresis, and spasticity (1). NAS often requires a prolonged hospitalization with an opioid taper (i.e., morphine or methadone) over multiple weeks (1, 3–6). The prevalence of NAS is 55%–94% of newborns whose mothers were addicted to or treated with opioids while pregnant (4). The average duration of hospitalization for neonates is 17 days (4).

The MOTHER study, called "the most rigorous comparison", (7) showed that pregnant women maintained on buprenorphine were retained at a lower rate, 67% versus methadone, 82%. Hospital stays for neonates lasted 10 days versus 17.5 days for methadone. There was a contingency management component to the study. Subjects were paid for urine drug screens negative for illicit drugs; average $1,500. Heroin use averaged 9 days in the last month, cocaine use 4 days. In addition, 85% of these subjects used tobacco.

The literature on psychotherapy during buprenorphine maintenance was reviewed by Carroll and Weiss in 2017 (8). Four studies that involved cognitive behavioral therapy or counseling had no impact on treatment retention or negative drug screens whereas four contingency management studies had a positive effect on these outcomes.

Tobacco use during pregnancy causes fetal loss, premature rupture of membranes, placental abruption, placenta previa, cleft lip/palate, cardiac, limb and gastrointestinal defects, low birth weight, and newborns with increased respiratory infections, bronchiolitis, otitis media, reactive airway disease, short stature, hyperactivity, obesity, decreased academic performance, and a 34% increase in unexpected infant deaths (7). Tobacco use in pregnant, opioid addicted women is high, between 88% and 95% (9). Tobacco cessation for opioid-maintained women is generally unsuccessful. Our review of the literature, and a 2015 review (10) found three studies. Two of these studies showed that none of these women were able to stop smoking. A 12-week contingency management study resulted in 31% cessation (11). However, it was unclear from the report whether the tobacco abstinence continued until delivery.

What the common comorbid psychopathologies in buprenorphine-maintained pregnant women might be is unexplored. We were unable to find any articles in PubMed regarding this question. One study of opioid use disorder patients receiving opioid substitution treatments showed more severe symptoms in women as measured by both general symptomatic index and symptom checklist 90-revised. Somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, phobic anxiety, and paranoid ideation were all more common (12).

We provide preliminary data from a case series employing a unique intervention. Our goal is to provide pilot data preliminary to a future study that incorporates a control group who receive conventional treatment.

METHODS

Study Design

This is a report of a retrospective chart review of 25 consecutive admissions over nearly four years, 2015–2018.

Participants

Every pregnant opioid addicted woman who presented for evaluation was taken into treatment. The SUNY Upstate Institutional Review Board (IRB) approved the study protocol. All subjects provided written informed consent prospectively which allowed us to use their de-identified information.

Baseline Assessment

A holistic evaluation of each pregnant woman resulted in DSM5 diagnoses, a dynamic formulation, and a treatment plan. Multiple pathologies were the rule, not the exception. Each diagnosis resulted in an identified treatment. If the patient had comorbid back pain and Attention Deficit Hyperactivity Disorder (ADHD), these immediately went into the treatment plan.

Every woman had to bring a support person for the initial evaluation. This required asking for help, and creating the start of a recovery environment, before arriving for evaluation. Usually, this support person was the mother of the patient, or the father of the fetus. Consequences of using other drugs were conveyed immediately to the patient and her supporters.

We use the cold pressor test to identify opioid induced hyperalgesia. This intensely experiential demonstration of opioids intensifying pain is shown by plunging the forearm into ice water. We used opponent process theory to explain how opioids intensify pain (13, 14) for our pregnant, opioid using patients with pain complaints. This intervention undercut idealization of opioid use and justification of opioid use for pain.

Psychotherapy was universal. Medications were added for ADHD, depressive disorders and tobacco cessation balancing the ideal of giving no medications if possible against the necessity of pharmacologic treatment for resolution of drug use in the context that abstinence is difficult while comorbid disorders are symptomatic.

Statistical Analysis

For comparisons between two categorical variables, p-values were generated using the chi-square test. For comparisons between two continuous variables, statistical significance was determined by an unpaired Student's t-test. Histograms show the mean values with standard deviation. The particular test used for each analysis is indicated in the figure legends. A p-value of < 0.05 was interpreted as statistically significant. All statistical analyses were performed using GraphPad Prism (version 7.0d).

Drug Use Targeted Therapy (DUST)

Theoretical Basis

DUST is an innovative psychotherapy developed by author Brian Johnson over a period of 5 years, using a theoretical-empirical approach. As we have described elsewhere, the scientific premise of our work, articulated in a theoretical model, posits that opioid use severely compromises the ability to relate because emotional contact is painful while maintained on opioids (15). Our approach took into account that our subjects were likely to experience that emotional contact involved in psychotherapy was aversive. Therefore, a contingency management could be built in, not by providing payment, but rather by allowing our patients to decrease the frequency of psychotherapy as a reward for abstaining from addictive drugs.

Therapeutic Alliance

We have not had an evaluation yet of an opioid addicted woman who was not also addicted to tobacco, often with cocaine, amphetamines, alcohol, and marijuana also used. DUST was built around the single treatment goal of a healthy baby—the agreed upon work of the pregnant patient, her supporters, and the treaters. The therapeutic alliance was constructed to include both benign and hostility-containing components. The initial alliance was built around agreement that the welfare of the baby is at risk if the mother continues her addictive drugs.

The emotional intensity of the healthy baby mandate was augmented by a fact sheet on effects of tobacco use on the fetus, read to the support person and treaters by the patient during the evaluation (**Supplementary Table 1**). The goal is to inform, but also to set the stage for psychotherapy done in the play mode, by listing a grim set of harms to the fetus from tobacco but ending with a wrong choice that tobacco use by the mother can also cause alien abduction. Although the topics of psychotherapy can be grim, the overall setting is fun rather than shame or judgment.

Warm and firm limits on drug use facilitate a holding environment. For example, one patient was positive for inhaling tobacco and cocaine on her first psychotherapy hour after intake. She said (jokingly), "What do you expect? I'm a drug addict!" Her baby's father was in prison and the father's mother had been the support person. A few weeks later her UDS was negative, she was ebullient, and said how proud the grandmother was about her efforts.

A urine drug screen (and since data collection for this contribution closed an expired carbon monoxide level) is done by the psychotherapist in front of the patient at the start of each DUST encounter. The results set the stage for the subsequent discussion of either abstinence or continued drug use by the patient.

Translating Behaviors Into Words

Another psychotherapeutic innovation is DUST's premise that drug use is "about something." There is a wild hostility in addictive behaviors (16). This is so apparent to lay observers that some states criminalize addictive drug use by pregnant women and it is considered child abuse in 18 American states (17). We fully subscribe to the hostility of addictive drug use by pregnant women and believe that the problem that allows it to continue is that the intent to harm the fetus is not conscious (18).

Interpretation allows the mother to make a conscious choice about whether to cause harm. With the fact sheet on tobacco use during pregnancy as a beginning, we can ask questions such as, "You know cigarettes are harming your baby, and you are still inhaling them. Tell me about that." Women were proud of the insights they developed from this investigation. For example, one woman whose mother had been abusive to her recognized that she had been unconsciously replicating that abuse by inhaling tobacco. Cigarette use stopped that moment. If treaters are not judgmental but rather curious, using the therapeutic alliance built in the first encounter and developed over a course of psychotherapy that all parties are deeply invested in a healthy baby as the outcome, women are able to turn malignant behaviors into safe words.

Making tobacco a central focus is not ideological but rather practical. Over the years, we have found that when patients stop tobacco, illicit opioids, and other addictive drugs almost always also stop.

Using Countertransference

The addicted person will often attack those who interfere with drug use. If addictive behavior stops, the hostility or other dysphoric experiences enter the relationship with the psychotherapist (19). Therefore, the psychotherapist must be able to tolerate feelings of rage, hate, and hostility both in the patient as they relate to others in their human surround and also as these feelings are stirred up in the countertransference experienced by the psychotherapist. The psychotherapist must master their own aggression and channel it into providing a holding environment that aggressively contains the patient's rage.

We helped our pregnant women be aware of their hatred and rage. We explained that it's expression as addictive drug use was hurting their fetuses. We used the power of providing buprenorphine as part of containing this hostility while using our

therapeutic alliance as a benevolent force. Women understood the shared goal to have them deliver babies who had to withdraw from buprenorphine only.

Combined Psychotherapy and Psychopharmacologic Treatment

In our review of combined psychotherapy/pharmacology treatments in addiction, we found few studies (20). Most treatments use medications alone or psychotherapy alone. DUST is delivered by medical practitioners who concordantly prescribe medications that propitiate abstinence. While buprenorphine maintenance is bedrock, difficulty with tobacco use cessation is targeted with medications such as bupropion and varenicline. DUST is a classic psychotherapy/medication combined treatment. If there is difficulty stopping tobacco, following a risk/benefit discussion about varenicline, the patient was asked to stop tobacco the night before, come to their psychotherapy hour craving nicotine, and take varenicline 0.5 mg in front of the psychotherapist. Nicotine craving disappeared in 20 min. The patient was told that any subsequent nicotine cravings could be responded to with more varenicline. Dosing is variable according to need. Varenicline effect lasts a few hours. The highest dose used in the case series was 3 mg/day taken in 0.5-mg doses. If tobacco is used in place of varenicline, this became a topic for psychotherapy. Other members of the household who are also addicted to tobacco are invited to participate in tobacco cessation treatment.

Because of reports of NAS provoked by the SSRI group of antidepressants or combined opioid/SSRI withdrawal (21) we discontinue SSRIs, evaluate subsequent depressive symptoms, and replace with bupropion if an antidepressant is needed. The general approach was to avoid prescribing anything but buprenorphine. Bupropion or varenicline were given if needed as an adjunct to DUST.

Contingency Management

Initial meetings were weekly. Buprenorphine prescriptions were issued for a week. We acknowledged how difficult it is to stop addictive drugs. Our contract was that if the use of all other addictive drugs besides buprenorphine did not end, as verified by urine drug screen and (since data collection ended) expired carbon monoxide after four weeks, we would only prescribe buprenorphine for 3 or 4 days at a time for the next four weeks, with DUST twice a week. If the drug screen was not negative at 8 weeks, DUST was daily 5 days per week with only 1 day of buprenorphine prescribed at a time.

When it proved difficult to stop drug use the attending psychiatrist provided his cell phone number and asked that the patient call BEFORE any more drug use. This did not cause any undue burden on the psychiatrist. The reason for this is that patients tended not to call, but to come back not using addictive drugs, as if they thought of calling and then did not use the drug.

Once the drug screen turned negative for everything except buprenorphine, we were in a continuation phase of treatment, the acute interventions were over, and visits became monthly. The only cotinine positive UDS we have found at this point have to do with second hand smoke exposure. The mother becomes aware of the hostility of her loved ones, furthering discussions of safety and health. Weekly psychotherapy continuation was offered, but nearly universally declined. Our understanding is that buprenorphine maintenance makes emotional contact painful (22). We take advantage of this phenomenon to make DUST a form of contingency management. The reward of decreasing painful emotional contact motivates the patient to remain abstinent.

Summary: Contingency management involves being allowed to come to treatment less often when UDS shows abstinence from addictive drugs.

Visit	UDS Result	Treatment Response
1	Pos	Come back in a week
	Neg	Come back in a month
2–4	Pos	Come back in a week
	Neg	Come back in a month
5–8	Pos	Come back in 3–4 days
	Neg	Come back in a month
9–Delivery	Pos	Come back 5 days/week
	Neg	Come back in a month

RESULTS

Patient Characteristics

The average (mean) age of the patients was 29 (range 20–36). Ten women were in the first trimester at intake, 10 in the second, 5 in the third. None of the pregnancies were planned, but all were desired once known. There are 14/25 women who gave a history of physical, emotional, or sexual abuse, and 10/25 had a history of criminal conviction. The cold pressor time was tested for 10/25. It averaged 23 s (range 0–72) in the context that 23 female controls on our service, average age 52, averaged a cold pressor time of 111 s (20). The average score on the faces pain scale for 23 women was 3.4 (range 0–9). In addition, 25/25 women used tobacco. Other substances used at intake were cannabis 6, cocaine 4, benzodiazepines 4, methamphetamine 2, alcohol 1.

Comorbid psychiatric disorders were: attention deficit hyperactivity disorder 10, borderline personality 9, major depressive disorder 3, persistent depressive disorder 3, anorexia nervosa 1. Most women were poor, disadvantaged and functioned at a low level psychologically. A total of 7 women were prescribed bupropion, 300 or 450 mg/day. Five women who could not stop tobacco without medication or with only bupropion were given varenicline.

Treatment Outcomes

One patient had a spontaneous miscarriage at 5 months gestation and was removed from data analysis. Four discontinued treatment. Of the remaining 20 patients all stopped tobacco. One patient insisted she needed sertraline and clonazepam. Her child had significant NAS. There are 19/20 women who stopped all

addictive drugs, 13/20 women were consistently negative for cotinine, and 7/20 were positive for cotinine but avidly insisted that they were no longer inhaling tobacco. What we have found since we began using a carbon monoxide meter is that women who are exposed to second hand smoke that have cotinine positive urines. They made comments such as, "My boyfriend smoked in the truck while he drove me to this appointment." At the time of delivery, women who were abstinent from addictive drugs were also in remission from depressive disorders.

While initial buprenorphine dose was indistinguishable between mothers whose children did and did not develop NAS, the minor NAS observed in the five women whose children did develop transient NAS was significantly related to dose escalation of buprenorphine (**Figures 1**, **2** and **Table 1**).

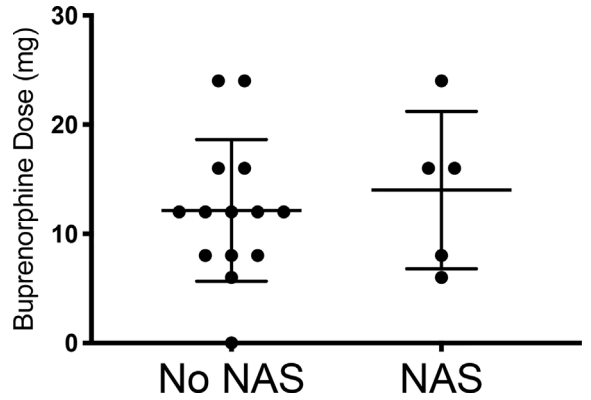

FIGURE 1 | Comparing the initial buprenorphine doses between patients whose infants had NAS v those who did not develop NAS. No NAS mean = 12.14 [Stdev 6.49] n=14; NAS mean 14.00 [Stdev 7.21] n=5; Two- tailed t-test [p=0.60].

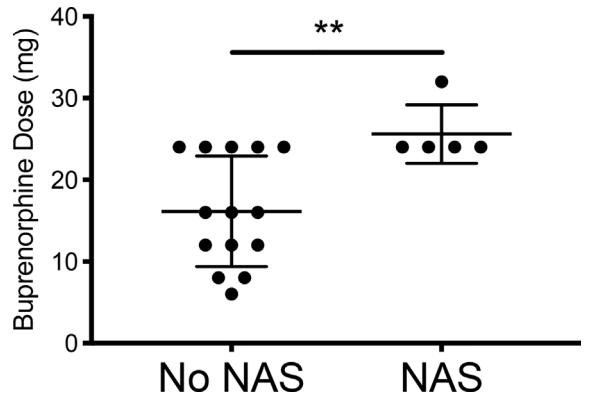

FIGURE 2 | Comparing the final buprenorphine doses between patients whose infants had NAS v those who did not develop NAS. No NAS mean = 16.14 [Stdev 6.77] n=14; NAS mean 25.60 [Stdev 3.58] n=5; Two- tailed t-test [**p=0.009].

TABLE 1 | Escalation of buprenorphine dose during treatment was significantly linked with NAS.

	NAS n = 5	No NAS n = 14	p-value	Test
Dose Escalation	4	6	0.15	Chi-Square
Initial Buprenorphine Dose	14.00 ± 7.21	12.14 ± 6.49	0.60	Unpaired t-test
Final Buprenorphine Dose	**25.60 ± 3.58**	**16.14 ± 6.77**	**0.009**	**Unpaired t-test**

The significance of the bolded data is p = 0.009.

DISCUSSION

Our main findings are:

1. DUST results in a high quit rate for addictive drugs. The high rate of quitting seems related to a sustained engagement in psychotherapy that takes into account the limitation of relatedness seen during opioid maintenance, beginning the treatment with clear education, a handout on tobacco shared with an important supporter, and then investigation of impediments to abstinence. Asking about the patient's thinking regarding injuring their growing fetus with drug use was regarded as a non-judgmental statement of fact supported by scientific evidence. The DUST intervention made conscious the hostility involved in drug use while pregnant and often helped transfer the hostility from the fetus toward the therapist. The therapist was then able to contain the aggression resulting in clinical improvement. The therapeutic alliance with play as the modality of engagement made it clear that the enemy was not the pregnant patient, but rather the entities who sell drugs.
2. What has sometimes been termed "neonatal opioid abstinence syndrome" may be combined drug withdrawal. It might most accurately be termed, "neonatal opioid/tobacco abstinence syndrome" because tobacco seems to be a significant factor in NAS intensity and duration. Tobacco seems to be the most common drug in terms of multiple drug use. If treatment brings tobacco use into remission other drugs are rarely used.
3. Contingency management is built in, not with financial payments, but by understanding that opioid maintenance makes human contact uncomfortable, informing treaters that the "reward" for abstinence can be allowing disengagement. This makes contingency management more widely available as a therapeutic technique. Like many other treatment programs that barely make our expenses, we would find it difficult to have financial payments as part of the care.
4. Part of the empathy involved from the treater side was that being engaged emotionally was tolerated by the patients because of their commitment to having a healthy baby. We appreciated that there were many difficulties involved in an ongoing treatment. Giving up drugs is hard, especially when pregnant!
5. Intimate partner violence is an important aspect to consider in terms of treatment (6). We extend the concept of intimate partner violence toward mother and fetus to include second hand smoke. Again, this is not a conscious hostility. A

negative exhaled carbon monoxide combined with a positive urine cotinine allows the pregnant patient to be more aware and to warn their emotional supporters, that environmental nicotine is getting into mother and fetus. Finding positive urine cotinine after inhaling cigarettes has stopped facilitates the pregnant woman to ask supporters to care for her and the fetus by avoiding smoking near her.

6. In contrast with an authoritative review that explained buprenorphine dose was not related to NAS incidence (6). when other drugs are removed, buprenorphine dose was correlated with incidence of NAS.

There are limitations to this study:

1. This was an exploratory case series developed on an Addiction Medicine service. It is only a preliminary report.
2. Results were collected as part of routine treatment rather than assessed by a blinded third party.
3. The case series is small.
4. There was no comparison treatment group.
5. Expired carbon monoxide was not measured. Cotinine positive urines obtained while the mother unequivocally stated that she had stopped nicotine use were counted as quits. Introduction of carbon monoxide meter after this case series closed revealed that persistent cotinine positive urine drug screens was probably caused by second hand smoke. However, it is possible that the self-report may have been dishonest.
6. Longer term outcomes of maternal health such as postnatal persistence of addictive drug use, overall health and competence to parent, as well as newborn physical health, appropriate developmental milestones, growth, and bonding between mother and infant, were not undertaken.
7. Generalizability of results to other treatment services cannot be addressed with our data.
8. Our literature review revealed that comparisons of our outcomes to other treatments is difficult because:
    a. There do not seem to be any reports of successfully helping pregnant buprenorphine-maintained women abstain from tobacco and other addictive drugs and,
    b. We could find no reports of treatment of comorbid psychiatric disorders in pregnant buprenorphine-maintained women.

CONCLUSION

We have created a novel intervention for pregnant opioid addicted patients on buprenorphine maintenance that is promising regarding cessation of addictive drugs and that may decrease the prevalence and severity of NAS. Compared to published outcome studies:

1. We are using a version of contingency management that does not require cash payments. The reward is distance from treaters. It makes the DUST approach applicable to treatment facilities such as ours that treat mostly poor patients and operate on a budget that would not allow payments that are commonly as high as $1,500 for negative urine drug screens (1).
2. DUST takes advantage of all available aspects of treatment; consideration by pregnant women about what drugs do to their fetuses in a supportive and non-judgmental environment without need for the therapeutic relational bond that dooms psychotherapy on buprenorphine-maintenance, (8) requiring patients to ask for help before they arrive, facilitating support for abstinence, and having a healthy baby, and medications such as bupropion and varenicline if needed, to help patients abstain from the decisive addictive drug, tobacco.
3. Even in the best available study, MOTHER, (1) retention on buprenorphine was 2/3, heroin use averaged 9 days in the last month, cocaine use 4 days and 85% of subjects used tobacco. Our very preliminary pilot study resulted in an unusually high retention rate, 80%, and abstinence for 95% of women followed through delivery.
4. NAS was reported by 5/19 of our abstinent subjects as present but a transient, less than a day, experience of newborns. This is far below the 55%–94% in other studies (4). None of the newborns was treated with opioid medications versus the vast majority reported in other studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because: Deidentified information was used but is not to be disseminated. Requests to access the datasets should be directed to johnsonb@upstate.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by SUNY Upstate Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ST and SH wrote the first draft. BJ's service is where the case series took place. He invented DUST. SS treated the first patients in the case series and contributed to writing. SM did the statistical analysis with input from SF, who also extensively wrote the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.563409/full#supplementary-material

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ORIGINAL RESEARCH
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Inhibitory Control and Craving in Dual Disorders and Recurrent Substance Use. Preliminary Findings

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Objective: In Dual Disorders (DD), which involves the co-occurrence of a disorder in substance use and a mental disorder, recurrent struggles with addictive behavior are frequent. Neuropsychological knowledge concerning the profile of inhibitory control and the irresistible urge to use substances (craving) within the DD patient group may contribute to the prevention of this recurrent addictive behavior.

Methods: Inhibitory control and craving were assessed in 25 patients with DD and 25 healthy controls (HC). Inhibitory control tasks (Go/No-go task and Stop Signal Task) were performed combined with brain measurements (Event Related Potentials) mapping inhibitory control. Moreover, implicit and explicit measures concerning craving were administered. Statistical DD and HC comparisons, correlational and regression analyses on exploratory base were conducted.

Results: DD patients committed more inhibitory control errors than HC when confronted with (alcohol) consumption-related picture stimuli. Furthermore, patients with DD showed higher levels of implicit and explicit craving. The number of inhibitory control errors was positively related to levels of implicit and explicit craving. Moreover, explicit craving and impulsivity (as a dimension of inhibitory control) predicted the severity of addictive behavior. Event Related Potential analyses did not show differences in inhibitory control-associated brain activity between DD patients and HC; both groups showed reduction of P300 amplitudes in response to alcohol pictures.

Conclusions: Impulsivity and craving are elevated in DD patients and show predictive value for the severity of addictive behavior. One's level of impulsive action tendency may trigger less effort to control (recurrent) substance use. The findings may contribute to existing DD treatment indications by the promotion of impulse control training via "stop-think-act" methods for DD patients.

Keywords: dual diagnosis, substance use disorder, event related potentials, P300, N200, executive function, impulsivity, dual disorders

INTRODUCTION

Failures to stop unhealthy behavior like substance use, and an irresistible urge for that use, seem central to addiction. Addiction can be described as an "enduring, inordinately strong tendency to engage in some form of pleasure producing or pain reducing behavior in a pattern that is characterized by (1) recurrent failures to *control* the behavior, and (2) *continuation* of the behavior despite significant harmful consequences" [(1), p. 270]. A better understanding of recurrent substance use behavior in addiction can be accomplished by analyzing it from the neuropsychological brain-behavior perspective. The brain-behavior model describes how brain processes direct and interact with neurocognitive functions and how these functions in turn direct and interact with human behavior (like substance use), while contextual factors can be of facilitating or disruptive influence on these brain processes, neurocognitive functions and behavior (2, 3).

The stopping failure in addiction and the mentioned urge to use substances, are respectively subsumed under the interrelated concepts of inhibitory control and craving (4). These concepts to date illustrate how patients that struggle with an addiction can perseverate in vicious circles of unhealthy behavior [see a review from (5)]. Recurrent substance use may count even more for patients with Dual Disorders (DD), which always involve a disorder in substance use, co-occurring with another mental disorder. The World Association on Dual Disorders advocates the term Dual Disorders. Another regularly used term with the same definition is Dual Diagnosis. DD combinations can have a shared cause, or can cause/intensify each other's utterance. For example, in many combat veterans a DD combination is present of a Post-traumatic Stress Disorder and a disorder in substance use. This combination may worsen the utterance of unhealthy substance use behavior (6). Higher levels of mood and temperament problems like hypomanic symptomatology correlate with higher co-morbid levels of substance use disorders, and with higher impulsivity and sensation seeking tendencies (7, 8).

Inhibitory control is a broad construct that encompasses biological (brain), cognitive, behavioral, and contextual aspects (4, 9–12). Deficits in inhibitory control are also seen as a reflection of impulsive action (13). In addition, on the brain level, inhibitory control and craving show neurobiological interrelatedness. Inhibitory control is an essential part of a Stop system in prefrontal and subcortical brain circuitry, which executes control by suppression of undesired responses. Whereas craving could be driven by a prefrontal cortex Go system which let's one engage in habits that can elicit an increase in dopaminergic effects (4). Because of the multifaceted character of inhibitory control and craving, assessment via multiple (both explicit or implicit) methods is the preferred strategy. Moreover, the use of multiple methods lines up the entire neuropsychological brain-behavior model (2, 3). Operationalization can be realized by use of neurobehavioral and electrophysiological instruments as well as through self-report.

Abbreviations: DD, dual disorders; ERP, event related potentials; HC, healthy controls; SUD, substance use disorder.

As to the electrophysiological measurement of inhibitory control, several studies have demonstrated that the Event Related Potential (ERP) technique is particularly valuable for bringing to light perception and attention processes (14). In particular, N200 and P300 ERP components have been associated with inhibitory control, and were studied thoroughly in substance use disorder populations [for a systematic review of the literature see (15)]. The N200 component is described as negative going amplitude, occurring approximately 200 milliseconds after the onset of a low-probability No-go-target within a highly probable Go-target context. The P300 component is described as a positive going amplitude peak that in turn occurs approximately 300 milliseconds after stimulus onset of a low-probability No-go-target (16, 17). Reduction of N200 and P300 amplitudes, have been shown for disorders in substance use, however, they are inconsistent for P300 amplitudes (most frequently assessed in alcohol use studies), and they are generally associated with behavioral dis-inhibition/poor inhibitory control (e.g., in No-go tasks) (15, 18–22). In the current study, a Go/No-go task is used to measure inhibitory control aspects, using a combination of alcohol related stimuli vs. non-alcohol related stimuli.

Since a substantial percentage of patients with SUD/DD show recurrent periods of substance use despite treatment programs, continuation of the search for a better understanding and control over factors that are involved in recurrent substance use remains relevant. So far, the number of studies that addressed inhibitory control and/or craving in a multi-method manner within a DD group of patients is limited, when compared to the number of studies in groups of patients that are solely described as having a disorder in substance use (23, 24).

The present study aims to contribute to the neuropsychological understanding of DD patients' persistent struggle with recurrent substance use behavior, by zooming into the neurocognitive function of inhibitory control and craving from a multi-method perspective, including both electrophysiological, neurobehavioral and self-report measures.

All of the above leads to the following main question of this study: do patients with DD, suffering from recurrent addictive behavior, show deficits in inhibitory control and/or show higher levels of perceived craving, as compared to healthy controls (HC)? And as a sub-question: are the levels of functioning on inhibitory control and craving interrelated, possibly also strengthening the severity of addictive (drinking) behavior?

Firstly, it is hypothesized that patients with DD indeed show more problems on inhibitory control measures and higher levels of experienced craving, as compared to HC. A large effect is expected on this part (4). Secondly, concerning the N200 and P300 ERP components as associated with inhibitory control, reduction of mean activity is expected for the DD patient group as compared to HC. That is, reduction of mean N200 and P300 activity is a sign for impairments in inhibitory control (15). Thirdly, as inhibitory control and craving show neurobiological interrelatedness in addiction (4) it is hypothesized that levels of experienced implicit and explicit craving in DD will show positive correlations with the amount of inhibitory control errors in DD. Thus: a higher amount of craving is expected to be related to

TABLE 1 | Descriptive statistics (Means and standard deviations for age, non-verbal intelligence screening, verbal intelligence screening) for dual disorders and healthy control groups.

Measure	Age		Verbal intelligence		Non-verbal intelligence	
Group	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Dual Disorders ($n = 25$)	41.80	11.97	95.20	7.90	113.70	9.09
Healthy control ($n = 25$)	40.96	13.71	99.60	10.82	117.96	8.87
Significance value	$p = 0.82$		$p = 0.11$		$p = 0.10$	

a higher number of inhibitory control errors on a Go/No-go task involving addiction-related pictures. The fourth hypothesis states that the interaction of inhibitory control and craving has a predictive value for the classified severity of addictive (drinking) behavior. Thus: the more inhibitory control errors one commits, and the more craving one experiences, the more severe one's daily life addictive behavior will be, classified on a substance use disorder identification test.

MATERIALS AND METHODS

Participants

Based on a power calculation [with G*Power 3.1; (25)] with an estimated effect size of d = 0.50, power of 1-ß = 0.80 and alpha = 0.05 for the DD and HC group comparisons, the sample sizes as recommended were 51 per group. Unfortunately, these sample sizes could not be attained within the study's data collection time frame (2014–2017) when adhering to inclusion/exclusion criteria like abstinence periods (also see procedure section below and discussion). Eventually, 25 patients with DD and 25 HC participated, fully meeting inclusion criteria. The DD group and HC group did not differ on mean age or intelligence (see **Table 1**). The DD group contained significantly more males than the HC group did (6 of 25 DD patients were female and 16 of 25 HC were female; $p < 0.01$). Therefore, sex was taken into account as an extra between-subjects factor in the analyses. In 23 of 25 DD participants, alcohol was a major part of the SUD (14 patients solely used alcohol as the substance of interest, nine patients used both alcohol and drugs, and two male patients solely used drugs. However, one of these two patients did earlier get into problems with alcohol use. DD's and substances of choice as present in the patient group are depicted in **Table 2**.

All participants were native speakers of Dutch, and had no neurological impairments or loss of consciousness ever in their life history. No Substance Use Disorders or other psychiatric impairments as assessed by clinical interviews (see below) were present in the HC group. All patients were substance-abstinent for a minimum of 6 weeks to prevent acute or sub-acute substance influences on cognitive functioning (26). Substance abstinence was mostly controlled for by alcohol/drug tests that were a regular part of the patients' treatments. The average substance abstinence period was 12.28 weeks (range from 6 to 32 weeks). All participants had normal or corrected-to-normal vision and sufficient reading abilities, and they showed intelligence scores of 80 or higher on both verbal and non-verbal capacity screening tasks (range 82–121 for verbal intelligence; range 96–127.5 for non-verbal intelligence). Total years of problematic substance use for the patient group ranged from 7 to 47 years and the starting age of substance use ranged from 11 to 28 years.

TABLE 2 | Demographic statistics DD group.

Dual Disorders and major substance of choice	Frequency
Mood disorder	9
Psychotic disorder	4
Personality pathology	21
Anxiety disorder	9
Attention deficit (hyperactivity) disorder	9
Developmental disorder like Autism spectrum disorder	3
Alcohol	14
Cannabis	1
Alcohol and cannabis	4
Alcohol and cocaine/speed	1
Cannabis and cocaine/speed	1
Poly use of alcohol and more than one kind of other drug	4

TABLE 3 | Materials as used for major paradigms.

Paradigm	Task
Inhibitory control	Go/No go task
	Stop signal task (SST)
	Barratt impulsiveness scale (BIS 11)
	event related potentials components N200 and P300
Craving	Obsessive compulsive drinking scale (OCDS)
	Alcohol urge questionnaire (AUQ)
	Alcohol-implicit association task (Alcohol-IAT)
Severity addictive behavior	Alcohol use disorder identification test

Materials

The major neurobehavioral, electrophysiological and self-report measures of use in this study are visualized in **Table 3**.

Tasks

Neurobehavioral Inhibitory Control Measures

Go/No-Go Task

The Go/No-go task consisted of a (1) Visual standard oddball Go part (Tea picture stimuli 80%, NoGo, Beer/Orange juice picture

FIGURE 1 | Pictures of the used Go/No-go task stimuli.

stimuli 10% Go), and (2) No-go-part (Tea 80% Go, Beer/Orange juice 10% No-go). The task was programmed in Delphi; a Go/No-go task by Matheus-Roth and colleagues served as an example (27). Matching on aspects like hue and luminance, took place when constructing the pictures, which are depicted in **Figure 1**. Each of the two task conditions was preceded by practice trials of 10 picture stimuli. Pictures were presented on a computer screen for 500 milliseconds (ms.), each, against a white background (screen resolution width = 1,024 pixels/height = 768 pixels/pixel depth = 16). A small fixation cross was presented for 2,000 ms. between the picture appearances, for the subjects to look at. During the two task conditions (Go and No-go) 312 pictures were presented to the participants in a randomized order, of which 80% (250) were (non-alcoholic) tea pictures, 10% (31) were alcohol-related pictures and 10% (31) were (non-alcoholic) orange juice pictures. In the Go-part, participants were asked to react to alcohol or orange juice pictures by pressing the button box, but not to react to tea pictures. In the No-go part, they were asked to react to tea pictures by pressing the button box, but not to react to alcohol or orange juice pictures. No feedback was given during the task concerning correctness of responses. Event Related Potentials (ERPs) as brain measure of inhibitory control were recorded during the task. The task administration time was approximately 26 min. The number of commission errors (push of button when no push was required), and reaction times (time in ms. between picture appearance and button push) were used for analyses.

Stop Signal Task [Part of Cambridge Neuropsychological Test Automated Battery (CANTAB)]

Measuring response inhibition, this task consisted of two parts. Initially, participants were asked to press the left hand button when a left-pointing arrow was shown on the screen, and press the right hand button when a right-pointing arrow was shown on the screen. Thereafter, the participants were told to keep pressing the buttons as before, but if they heard an auditory signal (beep), they should withhold their response and not press the button (www.cantab.com). The proportion of successful stops and reaction times (time between arrow appearance and button press) were used for analyses.

Self-Report Inhibitory Control Dimension Measure

Barratt Impulsiveness Scale-Eleventh Edition, Dutch Version (BIS-11)

The Barratt Impulsiveness Scale (BIS-11) is a questionnaire measuring aspects of impulsivity, with sufficient reliability and validity. Higher item-scores are indicative of a higher amount of impulsivity (some items being reverse-scored) (28, 29).

Brain Measures Inhibitory Control

Event Related Potentials (ERP), Mean Values of N200 and P300 ERP Amplitudes

In the present study, Event Related Potentials (ERP) data were collected during the Go/No-go task, in order to observe the P300 and N200 components that are associated with inhibitory control. The N200 was defined as the mean amplitude value (uV) in the 200-300 ms. time segment after onset of the response. The P300 was defined as the mean amplitude value in the 300-450 ms. time segment after onset of the response. Furthermore, N200 and P300 components have shown to be most evident on or nearby the EEG electrode sites Fz, FCz, Cz and C4 (for N200) and FCz, Cz, C3 and C4 (for P300) [among others, (30–32)]. Based on the combination of knowledge from this past research and on visual inspection of the current data, electrode sites Fz, C4, F3, and F4 were used for the N200, and Fz, C4, F3, and F4 were used for the P300 in the present study.

Craving Measures

Drinking Identity Implicit Association Test (Drinking Identity-IAT)

Lindgren and colleagues, described the Drinking Identity IAT as "a reaction time task that requires participant to rapidly classify stimuli into superordinate categories. The strength of participants' associations between those categories is posited to be indexed by the relative speed at which they classify stimuli into categories when the categories are paired to match vs. contradict their involuntary associations between those categories. Participants were asked to classify stimuli representing two identity "target" categories ("me" and "not me") and two drinking "attribute" categories ("drinker" and "non-drinker"). Drinker/partier/drink/ drunk suit the same category, and so do non-drinker/abstainer/sober/abstain, and me/my/mine/self and not me/they/them/theirs/other. The IAT consisted of 7 blocks, in which participants completed trials that contained single word stimuli presented in the center of the computer screen. The categories the participant could choose from for stimuli classification were at the left and right of the screen. There was no time limit for responses. Each pairing represented an association between the two (target and attribute) categories, and faster responses were indicative of a stronger association. For example, the target category of "me" might be paired in two blocks with the attribute category of "drinker" on the left of the screen, and "not me" with "non-drinker" on the right of the screen. In other blocks, this would then switch to "me" and "non-drinker" on the left and "not me" and "drinker" on the right. Faster reaction times in the blocks where "me" and "drinker" or "not me" and "non-drinker" were combined indicated a stronger association with these categories. Counterbalancing of blocks took place. The eventual IAT score of interest, the D-score (D-Biep), represented the standardized difference in average response time, and a higher score indicated faster response times when pairing "drinker" and "me." Adhering to recommendations in earlier research, IAT scores were excluded from analyses when individuals committed errors on more than 30% of the trials, or when participants completed 10% or more of the trials in 300 ms (33–35).

Obsessive Compulsive Drinking Scale (OCDS) and Alcohol Urge Questionnaire (AUQ)

The OCDS and AUQ are two questionnaires, used to assess experiences of craving [for the OCDS: (36, 37); for the AUQ: (38)].

Measures for the Identification/Severity of Mental Disorders

The M.I.N.I. International Neuropsychiatric Interview-Plus

The M.I.N.I. is a structured interview which measures the major psychiatric disorders as represented in the Diagnostic Manual for Mental Disorders. Validity and reliability measures point to sufficient values (39–42). Current diagnoses (or lack of them) were checked for DD and HC groups by assessment of the M.I.N.I. and by reading the patient files concerning diagnostic procedures that were followed earlier.

European Addiction Severity Index (EuropASI)

The interview was used to check the presence and severity of current and past Substance Use Disorders (43, 44). Furthermore, this interview measures problems in several life domains.

Alcohol Use Disorder Identification Test (AUDIT)

The AUDIT was developed and approved by the World Health Organization (WHO) as a self-rating measure to identify risky/damaging patterns of alcohol use, and it may also be seen as a measure indicating severity of addictive (alcohol drinking) behavior [(45, 46), Dutch translation by Schippers and Broekman (47)]. As outlined, most patients (23) used alcohol as a major part of their SUD, and one of the male patients that did not have a current disorder in alcohol use, did come into trouble with alcohol use in his past.

Procedure

Prior to the start of the study, approval for a broader neuropsychological project concerning self-regulation, where this study is a substantial part of, was obtained from the Radboud University Nijmegen Faculty of Social Sciences and its Ethics Committee for Behavioral Scientific Research (ECG; Protocol number ECSW2013-1811-148, letter number OOM/MB/13U.016587) and from the Vincent van Gogh Institutional Review Board (CWOP; Protocol U12.046). The research was performed in accordance with the principles of the declaration of Helsinki. Participants with DD were recruited by informing therapists in several departments of Vincent van Gogh Institute for Psychiatry (like addiction care and a department for Dual Disorders) about the scientific research. Consequently, patients, mostly hospitalized or in a 3 days a week ambulatory therapy program, were asked for voluntary participation by the main researcher. Freedom of choice to participate or refuse in this research was protected by securing absence of a therapist position of the main researcher to the patient that was asked. The advantage of primarily asking patients that were hospitalized or in a training program for several days a week, was that substance abstinence was regularly monitored by urine alcohol/drug testing. Healthy control group participants were recruited by means of social networking inside and outside the work institution; no psychologists were recruited, to prevent knowledge of the tasks of use in this study. Participants were provided with an information brochure detailing the study and consent form, which they read and signed. All assessed DD and HC participants were informed that they would afterwards receive a correspondence containing a broad descriptive strengths-and-weaknesses report of their results. Participants were selected on the basis of strict inclusion and exclusion criteria as previously outlined (see participants section). As a consequence of this, several DD and HC group participant data were eventually excluded from analyses, when exclusion criteria came to light on the assessment day itself (during the thorough assessments by the earlier mentioned M.I.N.I.-plus and EuropASI interviews), or when (even after succeeding test participation) any substantial hesitations were present concerning the reliability of patient's abstinence periods. Furthermore, exclusions from data analyses took place when

patients showed error numbers or response patterns that were signs of non-validity. Consequently, data of 30 patients in the DD group were eventually excluded: seven patients dropped out, for example, because of flu and lack of motivation to plan another appointment; nine sets of patient data were excluded because of lower-than-expected intelligence scores; for five patients neurological incidents in their history came to light during the interviews; of three patients a (not mentioned) lack of substance abstinence was revealed after testing took place by regular treatment urine samples; and six patients showed invalid/non-explainable extreme outlier profiles or missing data on questionnaires or neurocognitive tasks. The occurrence of (extreme) outliers was checked, by constructing box plots for the DD, HC and total group's data. Data were only excluded from analyses when the extreme outlier was interpreted as non-explainable/non-realistic (e.g., a high composite craving, or error score on base of several tasks may be realistic when no sign is present that the participant misunderstood the instruction and response form, or gave random responses on tasks, and did not fall within levels of non-valid error/reaction time-rates on tasks). For the HC group, data sets were excluded when present psychiatric disorders or problematic substance use (in past or present) came to light during testing day interviews (two participants), or when invalid/incomplete questionnaires or missing tasks were present (four). Eventually, valid data of 25 DD patients remained for analyzes and the number of assessed HC group participants was adjusted to that. Thus, 25 patients with DD and 25 HC fully met inclusion criteria and showed valid test results. Concerning the ERP data, 15 valid DD group data (12 males, 3 females) and 18 valid HC group data (7 males, 11 females) remained for analyses after artifact reduction took place. All participants were tested individually in a well-lit and undisturbed room which is part of the Center of Excellence for Neuropsychiatry, Vincent van Gogh Institute for Psychiatry; this location also included an ERP lab room. All tests were administered and scored, adhering to official test instruction manuals.

ERP Recording and Data Reduction

ERP data were recorded adhering to official procedures, and analyzed in accordance with earlier studies involving aspects of inhibitory control (N200 and P300). Thirty two electrode sites and an acti-CAP (Brain Products) with active Ag/AgCI-electrodes were used for the ERP recordings. Besides the ground and reference electrode sites, the following electrode sites were used: Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1 (Heog 1), FCz (Reference), FC2 (Heog 2), FC6, T7, C3, Cz, C4, T8, Tp9, Cp5, Cp1 (Veog), Cp2 (Veog), Cp6, Tp10 (right mastoid), P7, P3, Pz, P4, P8, PO9, O1, Oz, O2, PO10. All signals were digitalized with a sample rate of 500 Hz and 24 bit A/D conversion. Subsequently, the following analysis steps were followed: re-referencing of the data, filtering, segmentation, artifact reduction, baseline correction, calculation of subject and grand averages, and consequently the statistical analysis of data (48). Data were re-referenced offline to the right mastoid (as used regularly in ERP research). Electroencephalographic (EEG) activity was filtered with band pass of 0.10–30 Hz (phase shift-free Butterworth filters; 24 dB/octave slope). Segmentation took place in epochs of 1 s (200 milliseconds before and 800 milliseconds after the stimulus response). For ocular correction, the Gratton technique was used (49); epochs including an EEG signal exceeding ±75 uV were excluded from the average. As a baseline, the 100 ms pre-response period served. After baseline correction, average ERP waves were calculated for artifact-free trials at each electrode site for correct responses. As described earlier, the N200 was defined as the mean amplitude value in the 200–300 ms time segment after onset of the response. The P300 wave was defined as the mean amplitude value in the 300–450 ms time segment after onset of the response. Segments that contained incorrect responses were excluded from analyses (Go trails with incorrect responses, or No-Go trails with false alarms). As said, 15 valid DD group data (12 males, 3 females) and 18 valid HC group data (7 males, 11 females) remained for analyses after artifact reduction took place.

Data Analysis

SPSS version 25.0 was used for the statistical analyses. MANOVAs with bootstrapping and Bonferroni corrections (for multiple comparisons) were conducted to compare (composite) score differences between the DD and HC groups for inhibitory control and craving (50). Sex was used as an extra between-subjects factor in analyses. Repeated-Measures-ANOVAs (RM-ANOVAs) (with contrasts) were conducted to analyze performance outcomes on the Go/No-Go, and ERP inhibitory control indices. Between-subjects factors in RM-ANOVAs were group (DD vs. HC) and sex (male vs. female). Two-level within-subject factors were taken into account, namely Group × Inhibition (Go or No-Go) × Drink (Alcoholic or Non-alcoholic). For ERP analyzes three-level within subject factors were taken into account (Group × Inhibition × drink × Electrode). Lastly, Spearman correlation coefficients were calculated in order to analyze the relations between the concepts of inhibitory control and craving, and on exploratory base, binary logistic regression analysis was performed to check the predictive value of these concepts for the classified severity of addictive behavior (two categories of dependent variable severity of addictive behavior: a score of 14 or less, vs. a score of 15 or more on the AUDIT.

RESULTS

Main findings are presented for the DD group ($n = 25$) vs. the HC group ($n = 25$) concerning neurobehavioral and self-rating measures of inhibitory control, and measures of craving. Next, the ANOVA data for brain ERP measures of inhibitory control are presented. When a significant group × sex interaction effect is present, then group and sex findings are presented separately. Estimated marginal means and standard errors for the groups are presented. Finally, correlational and regression analyses are presented. For clarity, results from all analyzes are visualized by separate Tables and Figures.

Inhibitory Control and Craving

For group (DD vs. HC, see **Table 4**), a significant main effect was present on composite score measures of inhibitory control and craving, indicating that DD patients showed more problems in

TABLE 4 | Dual disorders vs. healthy control group composite scores and subscale scores comparisons with significance levels [(**$p = 0.01$; *$p = 0.05$); estimated marginal means, standard errors in parentheses].

Disorder scale	Dual disorders ($n = 25$)	Healthy controls ($n = 25$)	Significance ($p.$)
Inhibitory control total commission errors No-go	3.94 (0.65)	1.86 (0.58)	0.02*
Inhibitory control commission errors beer No-go	2.54 (0.44)	1.22 (0.40)	0.03*
Inhibitory control commission errors juice No-go	1.40 (0.32)	0.65 (0.29)	0.08
Mean reaction time Beer Go condition	393.96 (10.56)	391.85 (9.40)	0.88
Stop Signal Task proportion successful stops	0.53 (0.03)	0.50 (0.02)	0.35
Impulsivity BIS-11 composite score	69.62 (2.86)	54.39 (2.54)	<0.01**
Craving OCDS and AUQ composite score	12.82 (2.19)	0.59 (1.95)	<0.01**
Craving implicit measure IAT D-Biep	0.05 (0.14)	−0.32 (0.12)	0.05*

one or more of these domains than HC, $F_{(8,39)} = 3.61$, $p < 0.01$, Partial $\eta^2 = 0.43$). No significant main effect of sex, or Group × sex interaction effect was present.

The results demonstrated that DD patients had more inhibitory control problems than HC, in the form of a higher amount of commission errors on the (low frequent stimulus) No-go condition of the consumption related Go/No-go task [$F_{(1, 46)} = 5.77$, $p = 0.02$, Partial $\eta^2 = 0.11$]. And, in relation to specifically alcohol No-go trial pictures this DD-HC group difference in commission errors was present as well [$F_{(1, 46)} = 4.94$, $p = 0.03$, Partial $\eta^2 = 0.10$]. Moreover, patients with DD reported higher amounts of impulsivity, and higher levels of explicit and implicit alcohol craving than HC, as observed in composite scores (respectively $F_{(1, 46)} = 15.84$, $p < 0.01$, Partial $\eta^2 = 0.26$; $F_{(1,46)} = 17.46$, $p < 0.01$, Partial $\eta^2 = 0.28$; $F_{(1, 46)} = 3.96$, $p = 0.05$, Partial $\eta^2 = 0.08$). In contrast, no significant group differences were present for the number of errors committed on a non-consumption related inhibitory control task, and for reaction times on the Go/No-go task [respectively $F_{(1, 46)} = 0.89$, $p = 0.35$, Partial $\eta^2 = 0.02$; $F_{(1, 46)} = 0.02$, $p = 0.88$, Partial $\eta^2 < 0.01$].

ERP Data: P300 Component

RM-ANOVA analysis of the Go/No-go task P300 ERP component measure revealed a main effect for Inhibition (Go/No-go). Thus, the expected P300 amplitude peak actually occurred within the 300–450 millisecond post-stimulus No-go area as a reaction to the low frequency stimulus that required inhibitory control [see **Figures 2**, **3** and **Table 5**; $F_{(1, 29)} = 60.75$, $p = < 0.01$, Partial $\eta^2 = 0.68$)]. Moreover, a main drink x group x sex interaction effect was present [$F_{(2, 28)} = 3.89$, $p = 0.03$, Partial $\eta^2 = 0.22$]. That is, female DD patients showed reduced mean P300 amplitudes in reaction to alcohol pictures, when compared to female HC patients; however, this effect involves ERP data for which only three female DD data were present. Therefore, this effect was not further evaluated here. Furthermore, a main effect for drink, and an inhibition x drink interaction effect were present for the P300 component. That is, both patients with DD and HC showed reduced mean P300 amplitude in overall response (independent of Go/No-go conditions) to non-frequent alcohol related stimuli appearances (beer pictures) vs. non-frequent non-alcohol related stimuli appearances (juice pictures) [see **Figures 2**, **3** and **Table 5**; $F_{(2, 28)} = 8.13$, $p = <0.01$, Partial $\eta^2 = 0.37$]. Furthermore, the differences between mean P300 amplitudes on No-go and Go conditions were higher for both patients with DD, and HC when responding to the non-frequent stimuli, as compared to responses on No-go and Go conditions to high-frequency (non-alcohol) related stimuli (tea pictures) [see **Figures 2**, **3** and **Table 5**; $F_{(2, 28)} = 4.37$, $p = 0.02$, Partial $\eta^2 = 0.24$]. Finally, there was a main effect for the interaction of drink x inhibition x electrode x sex [$F_{(6, 24)} = 3.33$, $p = 0.02$, Partial $\eta^2 = 0.45$].

ERP Data: N200 Component

On RM-ANOVA analysis of the Go/No-go and N200 component ERP measure, no main group/sex/group × sex/other interaction effects were revealed at all. Therefore, no inhibition (Go/No-go) difference was present either, which indicates that the mean peak values of the N200, occurring in the 200–300 post-stimulus area in reaction on a low frequent stimulus that required execution of inhibitory control, did not differ from the mean amplitude values of the N200 in the 200–300 post-stimulus area as a reaction on a low frequent stimulus that did not require execution of inhibitory control [see **Figure 2** and **Table 5**; $F_{(1, 29)} = 1.43$, $p = 0.24$, Partial $\eta^2 = 0.05$]. However, there was a main effect for drink; in reaction to low frequent pictures of juice, the mean N200 amplitude value was higher (more negative) than the mean N200 amplitude in a reaction to high frequent tea pictures [main effect data: $F_{(2, 28)} = 3.41$, $p = 0.05$, Partial $\eta^2 = 0.20$; juice vs. tea data: $F_{(1, 29)} = 6.83$, $p = 0.01$, Partial $\eta^2 = 0.19$]. This difference was not present when comparing the mean N200 amplitudes of low frequent pictures of alcohol and high frequent tea pictures.

Relational Findings

When evaluating the DD group ($n = 25$) and relations between inhibitory control and craving, a positive relation was present between the amount of inhibitory control errors on the Go/No-go task and the level of self-reported impulsivity as part of inhibitory control (Spearman's rho 0.58**), and both explicitly and implicitly measured craving (Spearman's rho's respectively 0.45* and 0.59**). Higher amounts of inhibitory errors were related to reduced levels of mean P300 Beer-Go amplitude (for the C4 electrode, Spearman's rho −0.52*). A higher amount of craving was related to reduced levels of mean N200 Beer Go and mean N200 Jus Go amplitudes, most pronounced at the F3 electrode (Spearman's rho's 0.73** and 0.54*) (For findings also see **Figure 4**).

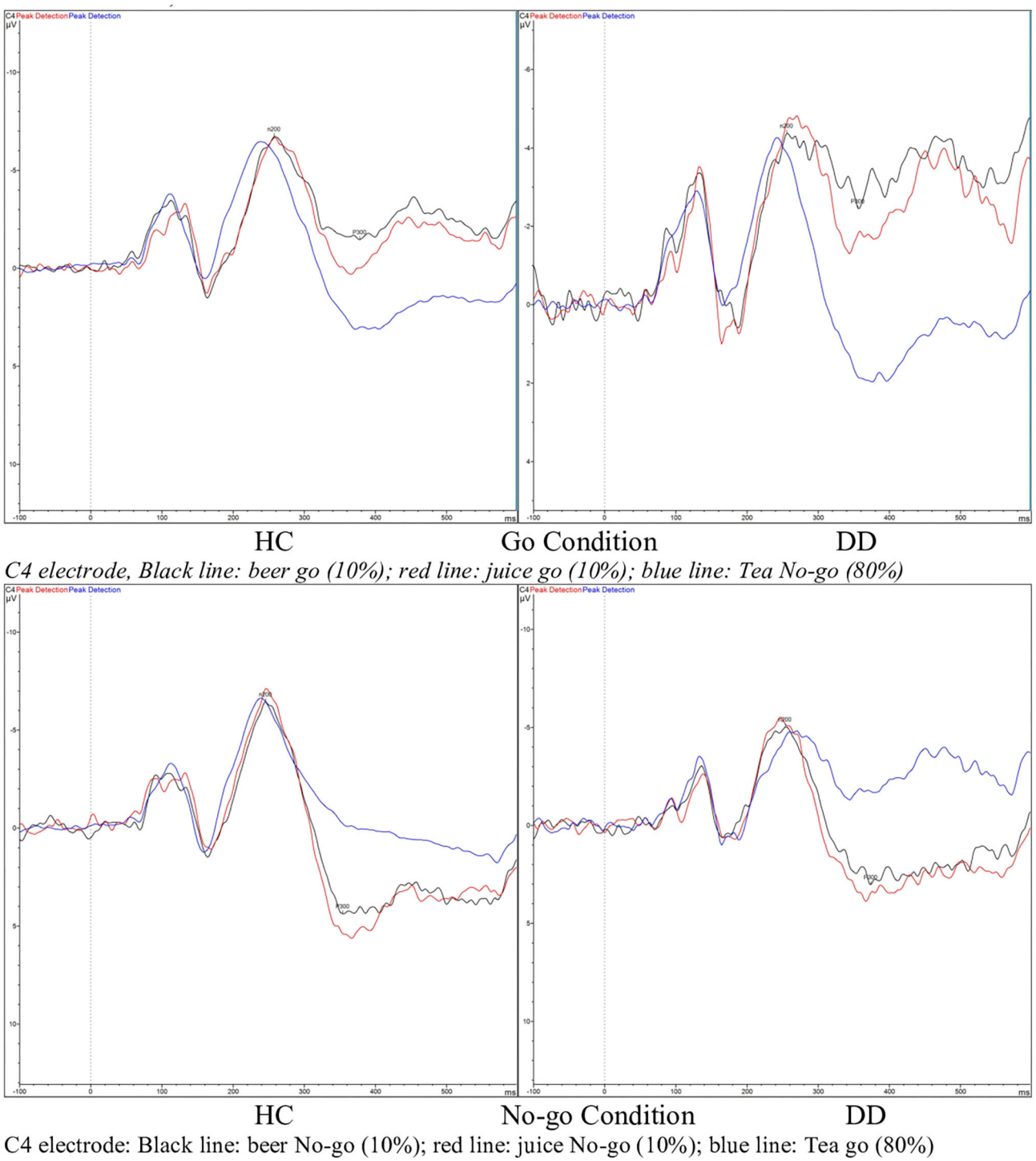

FIGURE 2 | Event related potential (ERP) graphs of P300 and N200 components for DD patients and healthy controls on a Go/No-go task, with alcohol-related and non-alcohol related stimuli, electrode C4.

Binary Logistic Regression Analysis

Finally, an exploratory binary logistic regression analysis was conducted for the whole group of participants, with the severity of addictive drinking behavior (AUDIT) as the dependent variable. Due to the low participant sample size ($N = 50$) a minimum of predictor variables was strived

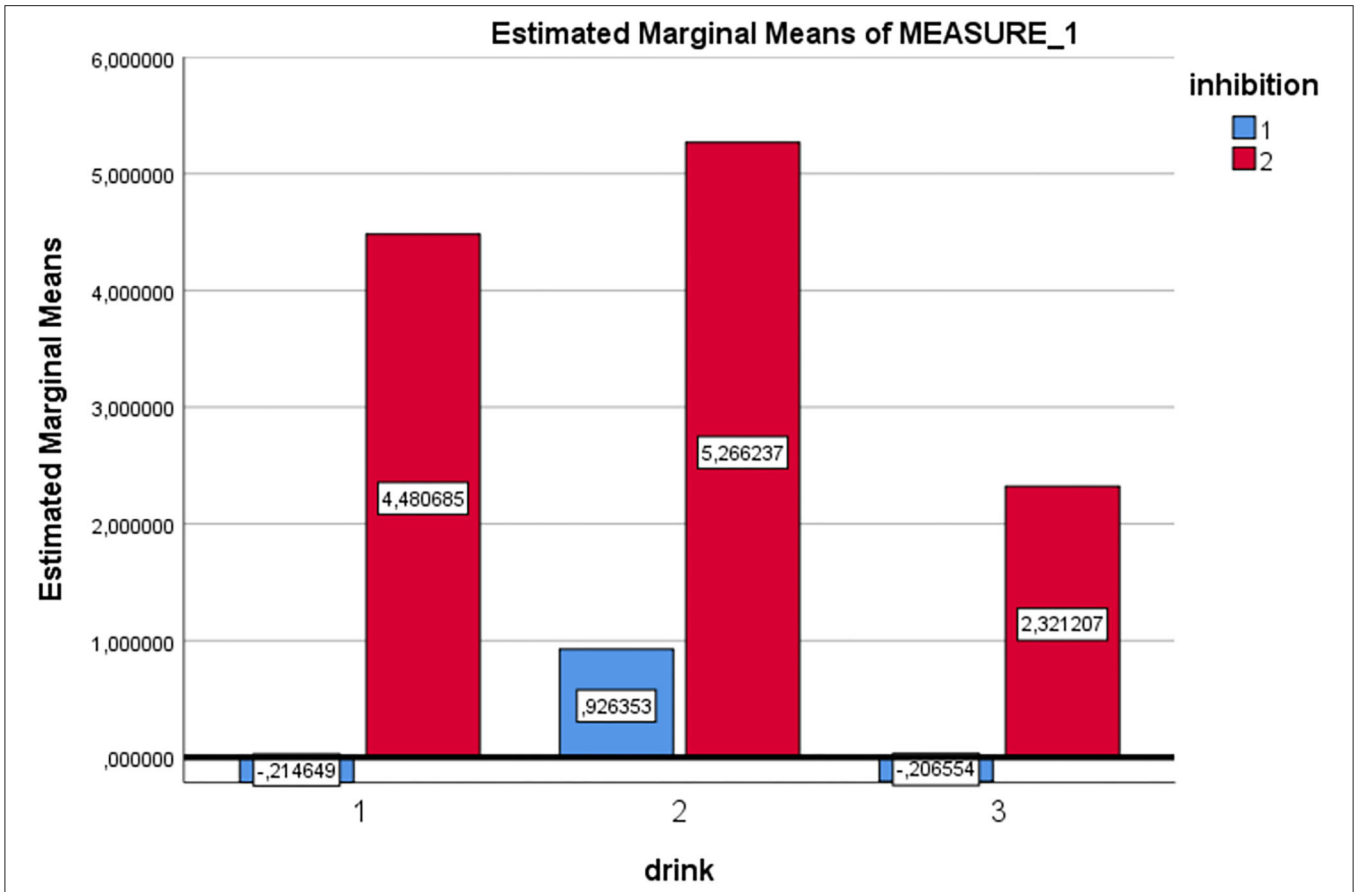

FIGURE 3 | Estimated marginal mean P300 amplitude values [Drink 1 = beer (low frequent), drink 2 = juice (low frequent), drink 3 = tea (high frequent), inhibition condition 1 = Go, inhibition condition 2 = No-Go (for all drinks in this graph)].

TABLE 5 | N200 and P300 component estimated marginal mean amplitudes for DD patients and HC.

		Controls	Controls	Patients	Patients
		Fz	C4	Fz	C4
Estimated marginal mean Amplitude value (estimated marginal mean, standard error in parentheses in uV)					
N200	Beer Go	−8.47 (1.08)	−8.34 (0.93)	−7.60 (1.44)	−6.81 (1.24)
	Juice Go	−8.08 (1.38)	−7.86 (1.16)	−7.81 (1.85)	−7.43 (1.54)
	Tea Go	−8.11 (1.17)	−7.51 (0.99)	−6.40 (1.56)	−5.64 (1.33)
	Beer No-go	−9.10 (1.44)	−7.94 (1.22)	−7.32 (1.92)	−7.00 (1.63)
	Juice No-go	−9.37 (1.51)	−8.41 (1.24)	−8.13 (2.01)	−7.47 (1.66)
	Tea No-go	−8.13 (1.22)	−7.11 (1.04)	−6.45 (1.63)	−4.74 (1.38)
P300	Beer Go	0.21 (1.16)	0.65 (1.20)	−1.44 (1.55)	−2.24 (1.61)
	Juice Go	1.33 (1.11)	1.74 (1.03)	0.16 (1.48)	−0.63 (1.38)
	Tea Go	−0.23 (0.83)	1.26 (0.90)	−0.81 (1.11)	−0.25 (1.20)
	Beer No-go	6.10 (1.46)	6.63 (1.12)	4.49 (1.95)	3.00 (1.50)
	Juice No-go	7.05 (1.61)	7.56 (1.19)	5.20 (2.15)	3.95 (1.59)
	Tea No-go	3.38 (0.97)	4.03 (0.72)	2.48 (1.30)	2.20 (0.96)

for. Therefore, initially the following independent variables were put hierarchically into the predictive model to test their contributive significance: impulsivity level, amount of inhibitory errors on the Beer no-go stimuli (Go/No-go task), level of explicit craving (composite craving score OCDS and AUQ), level of implicit craving (D-biep score IAT) and the interaction

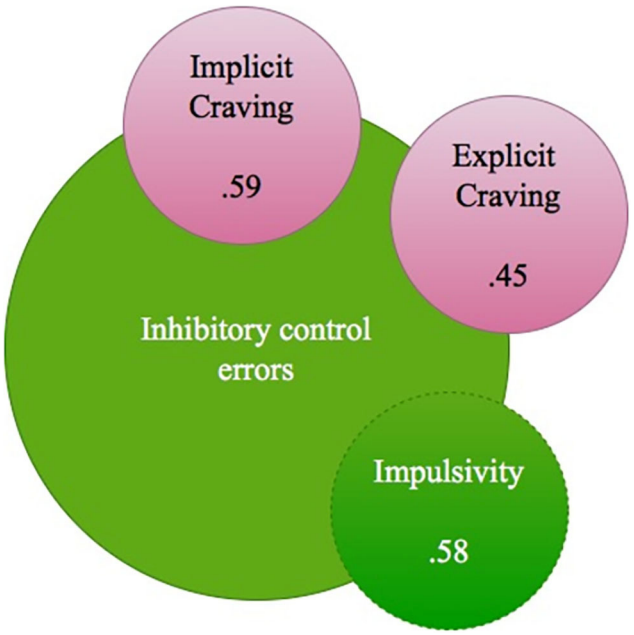

FIGURE 4 | DD group relations between Inhibitory control errors, impulsivity and (implicit and explicit) craving (Spearman's rho's).

of impulsivity level and explicit craving. The level of implicit craving variable and the interaction of explicit craving and impulsivity did not reveal significant contributions to the model independently and were therefore excluded from the model. Furthermore, tests for linearity of logits and multicollinearity were undertaken and revealed no issues. Eventually, the model with three predictor variables revealed a Chi^2 of 19.07 ($p < 0.01$), and the predictors accounted for 43.9 % of the variance in outcome (Nagelkerke R^2). See **Table 6** for an overview of findings. Summarizing, impulsivity and the level of explicit craving were of independent predictive value for a higher severity of addictive drinking behavior.

DISCUSSION

Aim and Main Question

This brain-behavior study aimed to contribute to the understanding of the recurrent addictive behavior in patients with DD, by zooming into the neurocognitive function of inhibitory control and into craving from a multiple method perspective. For this purpose, both electrophysiological, neurobehavioral and self-report measures were conducted within a DD patient and HC group. The main question was, whether patients with DD, suffering from recurrent substance use, demonstrate impaired inhibitory control and/or higher levels of craving, as compared to HC. Moreover, as a sub-question: are the levels of inhibitory control and craving interrelated, possibly also strengthening the severity of addictive (drinking) behavior?

Findings

As suggested in the first hypothesis concerning neurobehavioral inhibitory control and craving comparisons between patients with DD and HC, patients with DD did indeed commit more inhibitory control errors than HC on a Go/No-go task that involved consumption stimuli, and this was the case for alcohol pictures specifically. Interestingly, the finding solely occurred on this consumption related task but not on a non-consumption related stop signal task, and only when low frequent No-go picture stimuli were present in the context of high frequent Go picture stimuli. This finding may indicate that inhibitory control impairments of patients with DD are limited to substance-cue situations (like alcoholic stimuli), maybe specifically when these stimuli occur rather unexpectedly within the context. Whereas substance-abstinent DD patients may in general situations have sufficient inhibitory abilities. The second hypothesis, which expected N200 and P300 ERP data to reveal DD and HC differences in the form of reduced amplitudes in patients with DD, was not confirmed. ERP analyses did not indicate differences in inhibitory control-associated brain activity between DD patients and HC; both groups illustrated a reduction of P300 amplitudes in reaction to alcohol pictures. The third hypothesis was confirmed; that is, levels of implicit and explicit craving were both positively associated with the amount of errors in inhibitory control. This fits the literature that described the neurobiological interrelatedness of craving and inhibitory control in addiction (4). The fourth hypothesis stated that the interaction of inhibitory control and craving would demonstrate a predictive value for the classified severity of addictive (drinking) behavior. Thus: the more inhibitory control errors one commits, and the more craving one experiences, the more severe one's daily life addictive (drinking) behavior will be (as classified on a substance use disorder identification test). This hypothesis, via exploratory analysis due to the low participant sample size, was not confirmed. Explicit craving level and impulsivity (as part of inhibitory control) did indicate independent predictive values for the severity level of addictive behavior, but implicit craving level and the interaction of explicit craving and impulsivity did not reveal such predictive values.

The findings as demonstrated throughout this study do correspond with past research, including earlier developed addiction/craving models of Koob and Volkow (4) and Field and Cox (11). Relations between impaired inhibitory control and craving were confirmed, and specifically for consumer cues. This may also explain the lack of differences between the DD and HC group on a non-consumption related task in the present study. A recent large review concerning inhibitory control in (mostly recreational) substance use also revealed that inhibitory control is not per definition "overall" impaired for this behavior. And, when studying concepts, it is always necessary to be alert for potential confounders of findings. For example, sex differences between groups may influence results on measures of main interest (51).

Contributive of the present studies' findings to the existing knowledge concerning Dual Disorders and its recurrent substance use behavior, is that patients with DD demonstrate more impulsive tendency and impaired inhibitory control when confronted with consumption related stimuli, as compared to

TABLE 6 | Logistic regression analysis coefficients of the model, concepts predicting whether a participant showed a score of 15 or higher on the AUDIT (severity addictive drinking behavior).

Step 1	Wald	b	SE β	Exp. (β)	*P*	95% confidence interval for Exp. (β)	
Constant	9.51	−6.27	2.03	<0.01	<0.01**		
Impulsivity	7.29	0.09	0.03	1.09	0.01**	1.03	1.17
Explicit craving	4.17	0.14	0.07	1.15	0.04*	1.01	1.31
Inhibitory errors beer No-go	3.23	−0.52	0.29	0.59	0.07	0.34	1.05

*R^2 = 0.32 (Cox and Snell R Square), 0.44 (Nagelkerke R Square), Chi^2 (3) = 19.07 (Omnibus Tests of model coefficients), p < 0.01, Chi^2(8) = 10.48, (Hosmer and Lemeshow test) p = 0.23. Significance levels are stated as [(**p = 0.01; *p = 0.05)].*

HC. Further, levels of inhibitory control errors and craving are positively related. Moreover, the level of craving that is consciously experienced and impulsivity levels are of independent predictive value for the severity of addictive drinking behavior.

Electrophysiological (brain) data concerning the P300 and N200 ERP components did partly fit earlier data, as described in research studies and reviews from, among others, Luijten et al. (15). That is, the P300 did actually occur within the expected time area and expected P300 amplitude differences were present for responses to high-frequent and low-frequent stimuli, low-frequent stimuli evoking higher mean amplitudes [among others, in (16)]. But, there were no evident group differences with respect to the P300 and N200 components. The reduction in P300 amplitude is, as mentioned earlier, frequently associated with impaired inhibitory control. But, contrary to expectations, these reduced P300 amplitudes were present in response to alcohol related pictures for both Go and No-go trials, and in both the DD and HC group. In past craving research, larger ERP P300 components were signaled for patients with alcohol use disorders on alcohol related stimuli tasks. However, this was not revealed in the present study. The absence of a group effect could be explained by the fact that all patients with DD that participated were in (mostly intensive 24–7 or 3 days a week) treatment for their substance use disorders and were abstinent for substantial numbers of weeks (range 6 to 32 weeks). Thus, one possible explanation is that these patients with DD have already learned how to deal with thoughts of craving/show less differing P300 components as compared to HC. Elaborating on this, it may be a recommendation for studying the P300 component in the Go/No-go task within a DD group that is abstinent for a shorter period of time.

Limitations

Several limitations of this study need to be considered. The first major one concerns the effect sizes and sample sizes that were small (25 DD patients and 25 HC), when looking at the amount of variables taken into account and amount of analyses as undertaken. (Sub) group comparisons were underpowered due to this limitation and therefore were not included in this paper. As a consequence of all of this, conclusions should be taken cautiously and further research in larger patient groups is required. However, the execution of this study emphasizes the importance of clinical practice research, even when the gain of participants is a challenge and takes time and effort.

An additional limitation of the current study is the use of purely alcohol (and non-alcohol) related stimuli in the Go/No-go/IAT tasks and severity of addictive behavior measure (AUDIT) instead of a combination of alcohol and other drug related stimuli. However, for the majority of patients with DD alcohol was part of the substance use disorder (23 of 25 patients with DD, and 1 of the two male patients that only used drugs came into trouble with alcohol use earlier in his life). The decision for the use of the AUDIT score as estimate of the severity of addictive behavior, instead of the EuropASI interview score concerning the severity of substance use problems, was that the latter score is determined by the clinical review of the researcher that administers the task. In order to prevent any influence of biases in this research, the AUDIT score was used, which is fully determined by the answers the participant gives.

Finally, a significant sex difference that was present between the DD and HC groups resulted in a dilemma during ERP P300 data interpretation. Due to the limited number of valid female DD group data (3), this effect could not be accurately analyzed in order to draw conclusions from it. It deserves further research to perform comparisons between male and female DD patients on ERP measures (of inhibitory control in reaction to alcohol/non-alcohol related stimuli).

Future Research

Elaborating on the findings that impulsivity and craving have predictive value for a higher severity of addictive behavior, one could suggest that, when one tends to be more impulsive and urging, one regularly may want immediate gratification of desires like rewards or want alleviation of frustrations (52). That is, the tolerance for frustrations of impulsive and/or craving persons may be somewhat lower, triggering more (severe) recurrent substance use behavior to feel better. In light of this, a recent review from Sliedrecht et al. (53) revealed that the factor of gratification of desires is of minor influence on relapses in alcohol related behavior, whereas the urge for relief from unpleasant emotions is of more influence. Further research is required to test this suggestion concerning the relation between impulsivity, the urge for alleviation from frustrations and the severity of substance use behavior in a DD group. Furthermore, following up this study, Beerten-Duijkers et al. (54, 55) translated and adapted the Barkley Deficits in Executive Functioning Scales (BDEFS) for the Dutch language clinical practice. This self-rating questionnaire measures inhibitory control and impulsive tendencies as well as emotion regulation in reaction to potentially

frustrating situations. The BDEFS can thereby contribute to clarification of the relations between impulsive tendencies, emotion/frustration regulation and craving.

Furthermore, the gain of longitudinal data concerning recurrent substance use (e.g., number of relapses) leads to findings that link more to the real-world measure of inhibitory control impairments. That is, it would be interesting to see if the present findings, like the predictive value of impulsivity and explicit craving would also be translated in a higher level of relapses in addiction related behaviors.

Furthermore, the time of day at which a participant is tested can be of influence on functioning and therefore needs to be taken into account in future research (56). In the current research, the time of day was flexible, depending on the preference of participants in order to promote willingness to cooperate and to prevent drop outs.

Clinical Implications

Overall, this study's findings promote a better neuropsychological understanding of recurrent substance use in DD patients by measuring inhibitory control and craving. On the basis of the findings, additional attention is recommended for impulse control training within this patient group (training focused on Stop-Think-Act strategies). Training in this area may promote effective coping strategies for patients with DD who are particularly sensitive regarding impulsive tendencies that may eventually lead to severe substance abuse behavior. In currently available evidence-based treatment programs for addiction groups, craving is usually integrated already [for instance, in the Approach-avoidance training; (57, 58)]. However, as explained, a differentiated insight in one's functioning on addiction underlying concepts like inhibitory control and craving is of contributive importance for the understanding of one's strengths and pitfalls, next to more topographic knowledge concerning disorder classifications. When solely taking the latter as the lead, more standardized training accents might be used for a patient group as a whole, instead of keeping sight on one's specific needs in certain domains. An integrative view from the brain-behavior perspective transcends the topographic diagnostic classification knowledge and may thereby truly form a key contribution on the path to the stepwise prevention of recurrent addictive behavior.

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 Ethics Committee for Behavioral Scientific Research (ECG), protocol number ECSW2013-1811-148. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB-D performed the literature search, coordinated the data collection/analyzes and drafted the manuscript, together with CV. In addition, CV, MR, and JE were available for consultation and discussion during the project and during multiple rounds, revised the manuscript for important content. All authors contributed to the article and approved the submitted version.

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The Developmental Origins of Opioid Use Disorder and Its Comorbidities

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Opioid use disorder (OUD) rarely presents as a unitary psychiatric condition, and the comorbid symptoms likely depend upon the diverse risk factors and mechanisms by which OUD can arise. These factors are heterogeneous and include genetic predisposition, exposure to prescription opioids, and environmental risks. Crucially, one key environmental risk factor for OUD is early life adversity (ELA). OUD and other substance use disorders are widely considered to derive in part from abnormal reward circuit function, which is likely also implicated in comorbid mental illnesses such as depression, bipolar disorder, and schizophrenia. ELA may disrupt reward circuit development and function in a manner predisposing to these disorders. Here, we describe new findings addressing the effects of ELA on reward circuitry that lead to OUD and comorbid disorders, potentially *via* shared neural mechanisms. We discuss some of these OUD-related problems in both humans and animals. We also highlight the increasingly apparent, crucial contribution of biological sex in mediating the range of ELA-induced disruptions of reward circuitry which may confer risk for the development of OUD and comorbid neuropsychiatric disorders.

Keywords: early life stress, opioids, addiction, sex, anhedonia, reward, circuit, extinction

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INTRODUCTION

Opioid use disorder (OUD) is a growing epidemic in the United States and globally. To mitigate the rise in opioid-related morbidity and mortality, effective strategies are urgently needed to prevent the onset of opioid addiction by identifying individuals at high risk for developing OUD. Notably, OUD often occurs with psychiatric comorbidities such as depression, bipolar disorder, and schizophrenia (Brooner et al., 1997), all of which involve dysfunctional reward processing. Therefore, studying the basis for this disruption will provide greater understanding and insight into treating both OUD and its comorbidities.

The risk factors for OUD are numerous and complex, and genetics (Kreek et al., 2012; Crist et al., 2019; Jiang et al., 2019), drug availability (Volkow et al., 2011; Wright et al., 2014), and environmental factors such as early life adversity (ELA; Dube et al., 2003; Sinha, 2008; Kreek et al., 2012) all play a role. ELA related to poverty, trauma and chaotic environment affects over 30% of children in the U.S. (American Psychological Association, 2018). ELA is linked to numerous

long-term negative health consequences including obesity, heart disease, respiratory illnesses, as well as cognitive and emotional problems (Felitti et al., 1998), and it is associated with several affective problems that indicate dysfunction of the brain's reward circuitry (Kessler et al., 1997, 2010; Anda et al., 2006; Green et al., 2010; Pechtel and Pizzagalli, 2011; Novick et al., 2018). While a variety of the physical and mental health outcomes following ELA may lead to enhanced risk for OUD and its many comorbidities, here we focus on the effects of ELA on reward-related behaviors and underlying circuitry and propose that disrupted reward processing is a common developmental mechanism by which OUD and its comorbidities may arise following ELA. We also highlight the contribution of biological sex to the range of outcomes related to ELA-induced aberrations in reward circuitry.

NORMAL REWARD CIRCUIT DEVELOPMENT INVOLVES AN EARLY-LIFE SENSITIVE PERIOD

Reward circuitry in the brain is a network comprised of cortical and subcortical forebrain structures that regulate reward seeking. This circuitry is evolutionarily adapted to drive the acquisition of natural rewards, such as food, water, and reproduction. However, the maladaptive function of this circuitry can also lead to psychiatric manifestations such as mood disorders and addiction.

Whereas the reward circuitry has been extensively studied in the adolescent and mature brain, its function and developmental trajectory in infancy and early childhood are less well-known. The ventral tegmental area (VTA), nucleus accumbens (NAc), and amygdala, major nodes of the reward circuit, begin to appear in the first trimester in humans and around the second week of gestation in rodents, and continue to undergo significant maturation postnatally (Birnie et al., 2020). Behavioral manifestations of the reward function, such as responsivity to sucrose (Desor et al., 1973; Vigorito and Sclafani, 1988) and appetitive learning (Johanson and Hall, 1979; Hayne et al., 1986), emerge within the first months of life in humans and within the first postnatal days in rodents. These developmental timelines suggest that reward circuitry in a rodent in its first week of life might approximate that of a human neonate (Birnie et al., 2020).

The development of these circuits that occurs early in postnatal life suggests a possible sensitive period during which time aberrant environmental signals, such as parental abuse or neglect, may shape their developmental trajectories (Baram et al., 2012; Glynn and Baram, 2019; Luby et al., 2020). Analogous influences of critical environmental signals on network maturation are known for other circuits, including the visual and auditory (Zhang et al., 2001; Li et al., 2006). Just as these systems require predictable sensory inputs at specific times during development to mature properly, parental signals may provide important stimuli for the maturing reward system (Hane and Fox, 2016; Davis et al., 2017; Andersen, 2018; Glynn and Baram, 2019). Thus, understanding how the early environment alters reward circuitry will be critical for developing future interventions against OUD and other mental health problems.

DYSFUNCTION OF REWARD CIRCUITS: A COMMON THREAD FOR OUD AND ITS COMORBIDITIES?

The high prevalence of multiple diagnoses in patients with OUD (Kessler, 2004) supports shared or overlapping underlying processes and has led to searches for common genetic mechanisms (Carey et al., 2016). OUD is often diagnosed in patients who have other mental health problems (Brooner et al., 1997; Conway et al., 2006; Farrugia et al., 2011; Danovitch, 2016). Dysfunction of reward circuitry has been implicated in many of these other mental health diagnoses, such as depression and bipolar disorder (Russo and Nestler, 2013; Pizzagalli, 2014; Whitton et al., 2015), post-traumatic stress disorder (PTSD; Nawijn et al., 2015), personality disorders (Lawrence et al., 2010; Murray et al., 2018), and schizophrenia or psychosis (Kapur et al., 2005; Radua et al., 2015; Whitton et al., 2015). The specific comorbidities present with OUD also appear to be mediated by gender (Brooner et al., 1997; Conway et al., 2006). While women with OUD are more likely to also have a diagnosis of mood, anxiety, and eating disorders, men are more likely to have a diagnosed personality disorder (Brooner et al., 1997).

Notably, the prevalence of dual diagnoses is particularly high among patients who have experienced ELA, suggesting that ELA may impact a shared substrate involved in OUD and its comorbidities. In a study of patients admitted for chemical dependency treatment, those who reported a history of childhood abuse were also more likely to show symptoms of other reward-related comorbidities such as depression, bipolar, and anxiety disorders (Ellason et al., 1996). Another study found a very high co-incidence of PTSD and opioid abuse among women that was explained by a history of childhood trauma (Najavits et al., 1997). The risk for schizophrenia and psychosis is also increased by ELA (van Os et al., 2010; Bentall et al., 2014), which are highly comorbid with substance use disorder (Schmidt L. M. et al., 2011; Li et al., 2020). Palatable food cravings and disordered eating are strongly associated with ELA (Halmi, 2009; Dallman, 2014; Osadchiy et al., 2019), and these cravings are commonly observed in individuals with OUD (Morabia et al., 1989; Pelchat, 2002; Mysels and Sullivan, 2010; Canan et al., 2017; McDonald and Laurent, 2019; Nolan, 2019). This high co-incidence of multiple reward-related problems suggests a common underlying mechanism by which disruption of reward circuitry may lead to a variety of poor mental health outcomes.

DEVELOPMENTAL ORIGINS: ELA LEADS TO POOR NEUROPSYCHIATRIC HEALTH OUTCOMES

Numerous studies have linked ELA to poor cognitive (Lupien et al., 2009; Pechtel and Pizzagalli, 2011; Chen and Baram, 2016; Short and Baram, 2019) and emotional health (Heim and Nemeroff, 2001; Anda et al., 2006; Smyke et al., 2007; Maccari

et al., 2014; Callaghan and Tottenham, 2016; Hane and Fox, 2016; Krugers et al., 2016; Strathearn et al., 2020). For example, ELA is associated with lower educational achievement (Shonkoff et al., 2012) and poorer executive functioning abilities (McDermott et al., 2012). Evidence from clinical and epidemiological literature demonstrate links between adverse childhood experiences and increased risk for depression, anxiety, PTSD, eating disorders, and psychosis (Felitti et al., 1998; Chapman et al., 2004; Whitfield et al., 2005; Anda et al., 2006; Bale et al., 2010). The specific psychiatric outcomes resulting from ELA also vary by gender (Humphreys et al., 2015), with women more frequently diagnosed with anxiety and depression (Hammen et al., 2000; Heim and Nemeroff, 2001; Davis and Pfaff, 2014), whereas men are more likely to be diagnosed with personality disorders after ELA (Anda et al., 2006), the same pattern seen among those with comorbid OUD (Brooner et al., 1997).

Adverse childhood experiences are also robustly associated with later-life substance addiction (Nurco et al., 1996; Simpson and Miller, 2002; Dube et al., 2003; Widom et al., 2006; Gershon et al., 2008; Sinha, 2008; Enoch, 2011; Shand et al., 2011; Stein et al., 2017; Marsh et al., 2018). Results from the Adverse Childhood Experiences study show that ELA can increase the risk for injection drug use up to 11-fold (Anda et al., 2006) and that ELA increases the likelihood of early initiation of drug use independent of availability or changes in social attitudes towards drugs (Dube et al., 2003), suggesting a specific effect of adverse experiences on addiction liability. Additionally, individuals with a history of ELA are more likely to be prescribed opioid pain medications (Anda et al., 2008). This effect was mediated by an increased likelihood to experience other health and psychosocial problems, which highlights the interplay among the numerous physical and mental health problems associated with ELA, and the challenges in discerning causal mechanisms.

Interestingly, women appear to be particularly predisposed to OUD following ELA (Gershon et al., 2008; Lansford et al., 2010; Shand et al., 2011; Marsh et al., 2018). For example, although men have higher rates of overall substance dependence diagnoses, women who have experienced ELA are overrepresented among heroin and nonmedical prescription opioid users (Shand et al., 2011; Marsh et al., 2018). Women diagnosed with OUD are also two to three times more likely to have a history of PTSD related to ELA than men with OUD (Najavits et al., 1997). While this could be accounted for by the fact that girls tend to experience more childhood trauma than boys (Felitti et al., 1998), the magnitude of difference suggests a mediating role of sex. The type of adversity experienced may also interact with biological sex to affect outcomes. For example, Shand et al. (2011) found that emotional neglect during childhood predicted drug dependence in women, whereas PTSD predicted drug-related diagnoses for men. Again, the presence of other comorbidities varied by sex; men were more likely to display antisocial behaviors, whereas women were more likely to be diagnosed with anxiety and depression. These differences suggest divergent mechanisms by which ELA may alter reward circuit development between sexes, resulting in psychiatric outcomes that differ between men and women.

ANHEDONIA AND OUD, EACH MANIFESTATIONS OF REWARD CIRCUIT DYSFUNCTION, ARISE AFTER ELA

The paragraphs above suggest a strong association between ELA and malfunction of the reward circuit, which can manifest as OUD or other problems in reward-related behaviors. Many of these are common across several mental illnesses and may share common biological substrates. Anhedonia defined broadly as an inability to experience pleasure is a feature of substance use disorder in some individuals (Ahmed and Koob, 1998; Koob and Moal, 2001; Janiri et al., 2005; Hatzigiakoumis et al., 2011; Sussman and Leventhal, 2014; Kiluk et al., 2019; Brenner et al., 2020) and of other psychiatric diagnoses that are comorbid with addiction (Gorwood, 2008), such as depression (Loas, 1996; Blanchard et al., 2001; Pizzagalli et al., 2008; Martinotti et al., 2012), schizophrenia and psychosis (Andreasen and Olsen, 1982; Blanchard et al., 2001; Martinotti et al., 2012), PTSD (Risbrough et al., 2018), eating disorders (Davis and Woodside, 2002; Halmi, 2009), and other "high-risk" behaviors (Franken et al., 2006).

Indeed, the concept of anhedonia serves as a distinct useful transdiagnostic construct for understanding the role of altered reward processing in the etiology of psychiatric conditions (Bedwell et al., 2014; Lake et al., 2017). In line with the Research Domain Criteria (RDoC) framework put forth by the NIH, the ability to define a neurobiological basis of anhedonia, along with empirical behavioral measures both in humans and animal models, makes anhedonia a useful translational construct for studying reward circuit dysfunction and related behavioral disorders such as those seen after ELA (Cuthbert and Insel, 2013). Furthermore, the ubiquity of anhedonia as a feature of many of the psychiatric outcomes of ELA provides evidence that a mechanism by which ELA may impact cognitive and emotional health outcomes is through disruption of reward circuit development (Birnie et al., 2020). There are multiple domains of anhedonic behaviors that can be measured in humans and animal models which may have distinct neural processes (Der-Avakian and Markou, 2012; Shankman et al., 2014; Zald and Treadway, 2017). For example, anhedonia may represent a deficit in either anticipatory or consummatory reward, motivation, can be manifest for some reinforcers but not others (e.g., social vs. food rewards), and is also described as a feature of flat affect (for review, see Shankman et al., 2014). The neural substrates that govern these different forms of anhedonia have been explored (Gorwood, 2008; Der-Avakian and Markou, 2012; Treadway and Zald, 2013; Pizzagalli, 2014), and the specific effects of ELA on distinct types of anhedonic behaviors as well as their potentially dissociable neural substrates is an important area of continued investigation.

HOW DOES ELA PROVOKE ANHEDONIA, OUD, AND COMORBIDITIES? A NEED FOR ANIMAL STUDIES

While studies in humans offer important insights into the effects of ELA on reward circuitry, one cannot dissociate the

influence of early-life experiences on reward circuitry function from other genetic and environmental variables that may mediate the links between ELA, OUD, and other comorbidities. Animal models provide a method for investigating the effects of these environmental factors in isolation.

In animal studies, several different models of ELA have been used to isolate the effects of adversity on brain development from other genetic and environmental variables. These methods, such as maternal separation (MS), limited bedding and nesting (LBN), fostering by abusive caregivers, and others, have been extensively described elsewhere (Molet et al., 2014; Doherty et al., 2017; Walker et al., 2017; Wakeford et al., 2018; Brenhouse and Bath, 2019). In rodents and non-human primates, numerous studies have demonstrated that ELA results in behavioral phenotypes that suggest underlying dysfunction in reward-related brain regions (Molet et al., 2014; Andersen, 2015, 2018; Wakeford et al., 2018; Bonapersona et al., 2019; Birnie et al., 2020). The particular behavioral outcomes of ELA in animal models can vary depending on the type, timing, and duration of the paradigm, the species and strain of animal, and the timing and type of behavioral assays (Schmidt M. V. et al., 2011; Molet et al., 2014; Andersen, 2015; Walker et al., 2017; Brenhouse and Bath, 2019; Demaestri et al., 2020; Lundberg et al., 2020), as well as sex (Kundakovic et al., 2013; Bath, 2020). While this poses a challenge for interpreting this vast literature, the variability also mirrors human experience; indeed, ELA in humans can take many different forms, such as poverty, trauma, physical or sexual abuse, and neglect, and these, in combination with other environmental and biological factors, likely contribute to individual differences in clinical outcomes (Shand et al., 2011; Daskalakis et al., 2013; Sheridan and McLaughlin, 2014; Strathearn et al., 2020), highlighting the sensitivity of the brain to different types of stressors during these developmental periods.

Given that anhedonia has been associated clinically with many of the psychiatric outcomes of ELA, establishing whether ELA can actually *cause* anhedonia seems useful for determining neurobiological mechanisms that may ultimately underlie ELA-associated OUD and its comorbidities. Thus, we will highlight some animal studies that have focused specifically on anhedonia. The expression of anhedonia in animal models appears to be mediated by interactions between the ELA paradigm, biological sex, and testing parameters (Matthews and Robbins, 2003; Rüedi-Bettschen et al., 2005; Der-Avakian and Markou, 2010; Leussis et al., 2012; Lukkes et al., 2017; Di Segni et al., 2019). For example, in male rodents, ELA imposed *via* rearing for 1 week (P2-P9) in cages with limited bedding and nesting materials (LBN) leads to enduring anhedonia for both natural and drug rewards. This includes blunted sucrose and palatable food preference, reduced interest in social play, and decreased low-effort cocaine consumption (Molet et al., 2016; Bolton et al., 2018a,b). In contrast, such anhedonia is not observed in female rats after LBN (Levis et al., 2019). Yet, others have identified an age-dependent reduction of sucrose preference and depressive-like behaviors in female mice (Goodwill et al., 2019). Using a MS model of ELA, both male and female rats have reduced sucrose preference later in life (Matthews et al., 1996; Leventopoulos et al., 2009; Coccurello et al., 2014). Anhedonia has been reported also in nonhuman primates exposed to maternal deprivation and maltreatment (Rosenblum and Paully, 1987; Paul et al., 2000; Pryce et al., 2004; Kaufman et al., 2007; Glynn and Baram, 2019), such as reduced sucrose preference (Paul et al., 2000) or interest in social interaction (Coplan et al., 1996). However, others have found increased sucrose drinking in juvenile males (Nelson et al., 2009).

In contrast to natural reward anhedonia, other studies have demonstrated increased sensitivity to drug-related rewards (Andersen, 2018) as well as addiction-related behavioral traits (Hynes et al., 2018) after ELA. Although this may appear contradictory, these findings support the notion that the behavioral expression of altered reward circuitry by ELA depends on reward type and testing paradigm; thus, anhedonia and reward-seeking are not necessarily mutually exclusive.

While effects of ELA on increased alcohol and cocaine-seeking have been extensively studied and reviewed (Andersen, 2018), considerably less work has been done to model the effects of ELA specifically on opioid addiction vulnerability. Some evidence exists that MS increases morphine seeking in both male and female adult rats (Abad et al., 2016; Mohammadian et al., 2019) while others observed morphine preference only in MS males (Kalinichev et al., 2002; Vazquez et al., 2005, 2006; Michaels and Holtzman, 2008; Vey et al., 2016). Holtzman and colleagues show that male rats that have experienced MS demonstrate a greater place preference for morphine than their control counterparts (Michaels and Holtzman, 2008) and increased locomotor sensitization to repeated morphine, a measure of the psychoactive properties of the drug (Kalinichev et al., 2002). However, others have found attenuated sensitivity to the rewarding properties of heroin in MS females (Matthews and Robbins, 2003). Using the LBN model of ELA, we have demonstrated that, while males develop anhedonia for natural rewards like social play, palatable food, and sucrose (Molet et al., 2016; Bolton et al., 2018a,b), females developed a strikingly different phenotype (**Figure 1**). LBN females exhibit a marked increase in addiction-like seeking for opioid drugs (Levis et al., 2019). These rats were resistant to the extinction of opioid-seeking behavior, had stronger cue-induced and heroin-primed reinstatement responses, and increased motivation to self-administer the opioid remifentanil in a translationally relevant task measuring economic demand (Treadway et al., 2009; Bentzley et al., 2013; Bickel et al., 2014), demonstrating a motivation to obtain the drug even at a very high cost. Motivation for consuming palatable food was also significantly higher in LBN females, concurrent with the marked increase in addiction-like seeking for opioid drugs. Notably, this same phenomenon has been observed among patients seeking treatment for OUD (McDonald and Laurent, 2019).

Together, the findings in rodents and non-human primates suggest that ELA disrupts the maturation of reward circuits, and the resulting behavioral manifestations may vary by the timing, duration, and nature of the ELA and be further modulated by sex. Whereas deficits in reward-seeking behaviors are observed in males, such deficits are not commonly found in females. Rather, in females, the prevailing phenotype includes the enhanced consumption of opioids (and other drugs of abuse) and palatable

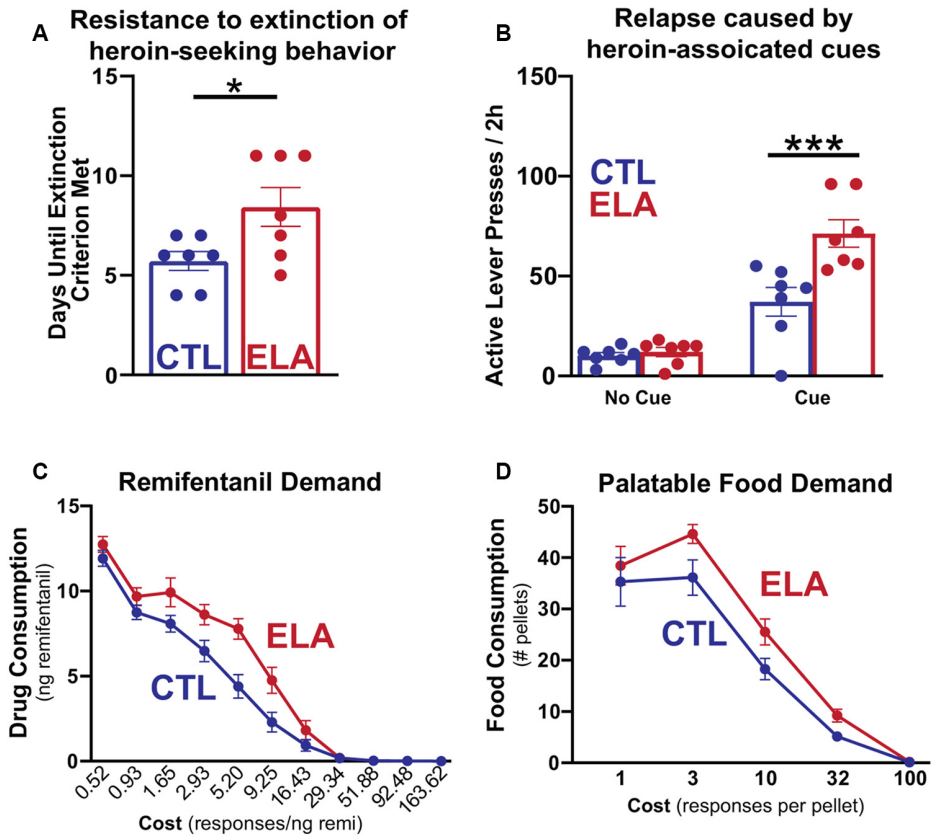

FIGURE 1 | Early life adversity (ELA) augments opioid-seeking behaviors and increases the demand for opioid drugs and highly palatable food. Adapted from Figures 1, 2 in Levis et al. (2019). **(A)** Female LBN-experienced (ELA) rats trained to self-administer intravenous heroin engage in more persistent heroin-seeking behavior after the withdrawal of the drug and **(B)** augmented relapse induced by heroin-associated cues than their control (CTL) counterparts. **(C,D)** On an economic task measuring sensitivity to increasing cost to obtain the desired reward, ELA rats are willing to exert more effort to access both opioid drug and food rewards at a higher cost than controls. This indicates increased demand for opioids and highly palatable food that is relatively insensitive to high costs. $^{*}p < 0.05$; $^{***}p < 0.001$.

food. The mechanisms underlying this phenotype are poorly understood and may involve ELA-induced changes in both reward and stress circuits. Support for this notion is provided by studies showing that female rats that have experienced stress tend to engage in more pro-hedonic consumption of palatable food (Dallman et al., 2003, 2005; Pecoraro et al., 2004; Jahng, 2011, 2014; Tomiyama et al., 2011; Machado et al., 2013; Kim et al., 2015), and that this may be specifically associated with anhedonia (Jahng et al., 2012; Jahng, 2014). Much information is needed to gain insight into the bases of palatable food craving as sex-dependent comorbidity of OUD.

Furthermore, the variable consequences of ELA on distinct assays of reward-seeking behaviors in animal models demonstrate that reward processing is not a singular phenomenon; rather, individuals may express different and dissociable phenotypes that suggest potentially discrete mechanisms of reward circuit disruption. Thus, further investigation into how ELA alters specific aspects of reward processing and underlying neural substrates will be critical for understanding the biological processes that contribute to the risk for OUD and comorbid disorders.

HOW MIGHT ELA LEAD TO OUD AND RELATED DISORDERS? EVIDENCE FROM CLINICAL IMAGING STUDIES

Evidence from human imaging studies suggests impaired development of specific reward-related brain regions and circuits after ELA that impose a risk for substance abuse and related comorbidities. Many studies have demonstrated functional and neuroanatomical effects of ELA on brain regions involved with reward and reward-learning, such as the hippocampus, amygdala, medial prefrontal cortex, and striatal areas including nucleus accumbens (Bremner, 2003; Hackman and Farah, 2009; Rao et al., 2010; Pechtel and Pizzagalli, 2011; Gee et al., 2013; Boecker et al., 2014; Callaghan and Tottenham, 2016; Teicher et al., 2016; Miguel et al., 2019; Herzberg and Gunnar, 2020). Childhood maltreatment is associated with blunted activation of these brain regions during reward processing tasks (Dillon et al., 2009; Mehta et al., 2010; Goff et al., 2013; Novick et al., 2018), a potential functional mechanism explaining the presence of anhedonia among individuals who have experienced ELA. Of these, the striatum appears to be especially important in

mediating the link between reduced reward reactivity and ELA (Dillon et al., 2009; Goff et al., 2013; Goff and Tottenham, 2015; Egerton et al., 2016; Kamkar et al., 2017; Dennison et al., 2019). The ventral striatum in particular seems to be a key mediator between ELA, anhedonia, and substance abuse. Corral-Frías et al. (2015) report that reduced reward reactivity in the ventral striatum predicts ELA-associated anhedonia and structural equation modeling revealed that this relationship also predicts substance-related coping behaviors, such as self-medication. This finding highlights a possible common mechanism by which ELA can lead to OUD and its comorbidities. The type of adversity experienced may also mediate the striatal response to reward (Dennison et al., 2019; Herzberg and Gunnar, 2020), as ELA in the form of childhood poverty, specifically, is associated with increased reactivity to reward in the striatum (Gonzalez et al., 2016), especially in girls (Romens et al., 2015). These sex- and experience-dependent differences are consistent with the observed variability of mental health outcomes in humans and behavioral phenotypes in animals.

ELA CAUSES FUNCTIONAL AND ANATOMICAL CHANGES IN REWARD-RELATED BRAIN REGIONS: EVIDENCE FROM ANIMAL MODELS

Building on clinical evidence, studies using animal models provide tools for identifying mechanisms that underlie disruptions in reward circuitry after ELA. In analogy to human literature, these outcomes appear to be partially mediated by sex. In males, our group has previously shown that anhedonia after LBN is associated with altered functional connectivity between the amygdala and mPFC in rats that may be mediated by CRH expression in the amygdala (Bolton et al., 2018a). This is supported by evidence that depressive-like behaviors and natural reward anhedonia following LBN are associated with disrupted amygdala-PFC and PFC-striatal functional connectivity (Yan et al., 2017). Additionally, Walker et al. (2017) have observed morphological and functional changes in the basolateral amygdala (BLA) and reduced functional connectivity between BLA and PFC in LBN-exposed male rats (Guadagno et al., 2018a,b). MS-induced ELA alters the development of PFC→NAc projections and dopamine (DA) signaling within the pathway in male rats (Brenhouse et al., 2013). In females, MS induces early maturation of the BLA-PFC circuit (Honeycutt et al., 2020), and early life social stress alters resting-state functional connectivity in NAc, hippocampus, and PFC (Nephew et al., 2017). In nonhuman primates, maltreatment during infancy leads to increased amygdala volume (Howell et al., 2014) and altered connectivity in regions implicated in mood disorders (Howell et al., 2013). c-Fos mapping studies measuring neuronal activity further suggest specific ELA-induced alterations in reward circuit function (Rincón-Cortés and Sullivan, 2016; Bolton et al., 2018a,b; Di Segni et al., 2019). Specifically, ELA leads to reduced NAc c-Fos activation in response to typically-rewarding stimuli like a social interaction (Rincón-Cortés and Sullivan, 2016), or aberrant over-activation of other regions associated with stress and reward (Bolton et al., 2018a,b).

Molecular mechanisms mediating the effects of ELA on OUD and related comorbidities may involve alterations in neurotransmitter and neuromodulator systems. Whereas a comprehensive discussion of this important topic is beyond the scope of this review article, a few salient points are mentioned: A vast literature documents the role of DA signaling in motivated and reward-seeking behaviors. Altered DA signaling is an important mediator of drug-seeking (Koob, 1992) as well as other psychiatric problems associated with ELA such as mood disorders (Diehl and Gershon, 1992) and psychosis (Kapur et al., 2005) and has been implicated in the expression of anhedonia (Willner et al., 1992; Pizzagalli, 2014). ELA has been extensively linked to dysfunction of the DA system in rodents, especially in the striatum (for a comprehensive review of this literature, see Bonapersona et al., 2018), and this may be mediated by alterations in other stress and reward-related transmitter systems (Forster et al., 2018). Additionally, the effects of early life experiences on DA signaling may be more pronounced in females (Camp et al., 1984; Chocyk et al., 2011). It is therefore tempting to speculate about the role of ELA-provoked deficits in DA signaling as involved in ELA-related OUD and its comorbidities.

Endogenous opioids play an important role in mediating hedonic processes (Smith and Berridge, 2007; Mahler and Berridge, 2009, 2012; Mitchell et al., 2018) as well as social attachment early in life (Panksepp et al., 1980), so the endogenous opioid system might also represent an important link between ELA and reward-related outcomes later in life. Alterations in opioid receptor mRNA have been observed in both males and females after ELA, although differentially between the sexes. Chang et al. (2019) show female-specific increases in NAc mu and delta-opioid receptor mRNA levels in mice after early life predator odor exposure. Nylander and colleagues have found long-term alterations in endogenous opioid peptides and opioid and DA receptor expression in reward-associated areas that vary both by sex and by the duration of MS (Ploj et al., 1999, 2001, 2003a,b; Ploj and Nylander, 2003; Gustafsson et al., 2008). Opioid receptors are known to modulate striatal DA signaling (Mulder et al., 1984; Johnson and North, 1992), an effect that may be potentiated by ELA (Karkhanis et al., 2016). Thus, disturbances in endogenous opioids might also mediate ELA-induced alterations of striatal DA signaling leading to aberrant reward-related behaviors. These ELA-induced opioids and DA-related disruptions suggest a mechanism by which ELA may lead simultaneously or in parallel to psychiatric disorders and enhanced consumption of opioids (Khantzian, 1987; Dallman et al., 2005; Kim et al., 2015; Lovallo et al., 2018).

Together with evidence from human subjects, these findings demonstrate that ELA alters important reward-related circuit nodes to provoke vulnerability to poor psychiatric outcomes. Establishing causality between network- and molecular-level changes induced by ELA and resulting reward-related deficits remains an important area of investigation to cure OUD and its psychiatric comorbidities.

CONCLUSION

Evidence across species suggests that ELA during sensitive developmental periods alters the developmental trajectory of reward circuitry. The precise nature of ELA, the potentially disparate consequences of different types of ELA, and the mechanisms underlying the aberrant maturation of reward circuits remain topics of much-needed investigation. The resulting maladaptive reward processing is likely a mechanism common to OUD and its comorbidities. As both animal and human studies demonstrate, the manifestations of this aberrant reward circuit function are varied and depend on the type and extent of adversity, biological sex, and later life experiences. However, functional, anatomical, and molecular disruptions in reward-related brain regions such as the medial PFC, striatum, and amygdala have been described across multiple paradigms and several species, suggesting a common developmental origin. Likewise, anhedonia may be an important behavioral biomarker of disturbed reward processing that links ELA, OUD, and other mental health problems. Further investigation into the neurobiological basis for ELA-induced reward circuit disruptions will provide key insights into the origins of OUD and its comorbidities and may uncover new interventions that will be successful in treating both.

AUTHOR CONTRIBUTIONS

SCL drafted the review. SVM and TZB guided the writing process and provided revisions. All authors contributed to the article and approved the submitted version.

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Non-medical Use of Prescription Stimulants Among College Students: Non-oral Routes of Administration, Risk Factors, Motivations, and Pathways

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Introduction: Non-medical use (NMU) of prescription stimulant medications is a continuing public health concern. Stimulant medications prescribed for attention-deficit/hyperactivity disorder (ADHD) are widely available on college campuses, and, as a consequence, college students may have multiple opportunities to engage in prescription stimulant NMU. This online self-report survey examined prescription stimulant NMU among college students, including: (1) patterns of non-oral route of administration (ROA); (2) motivations for non-oral ROAs; and (3) retrospectively recalled pathways of initiation.

Method: The survey sample was created from a pool of 3,379 respondents, who were matched to a sampling frame constructed from the 18–26-year-old, college student sample of the 2016 American Community Survey (ACS). About 14% ($n = 486$) from the overall pool were identified as college students with self-reported prescription stimulant NMU, all of whom completed the survey. The survey covered user characteristics, prescription and illicit substance use, age of first NMU, motivations for NMU, sources of procurement, and ROAs used.

Results: Among 486 students reporting prescription stimulant NMU, 43% had a lifetime diagnosis of ADHD. More than 90% reported polysubstance use, with 55% using illicit substances other than marijuana. Slightly more than 2 in 5 (43.3%) reported using illicit substances prior to prescription stimulant NMU, 24.6% used both at the same age, and 32.0% engaged in NMU of prescription stimulants prior to using illicit substances. Prescription stimulant NMU preceded prescription opioid NMU 45% of the time. More than a quarter of those engaged in prescription stimulant NMU (27.9%) initiated prescription stimulants alone or at the same age as other drugs. Most prescription stimulant NMU was oral, however 23.0% reported any non-oral use: snorting (20.4%), smoking (6.0%)and/or injection (3.5%). Non-oral use was associated with being male, obtaining medication from a dealer, use to get high, and/or a substance use disorder diagnosis.

Conclusions: Prescription stimulant NMU often occurs in the larger context of other substance use among college students. Injection, an under-researched route for prescription stimulants, was associated with male gender, history of substance use and higher likelihood of illicit substance use. Nearly a quarter of college student survey respondents reported use with non-oral routes, which is associated with other high-risk behaviors. Efforts to reduce non-oral prescription stimulant NMU in college students are warranted.

Keywords: attention deficit/hyperactivity disorder, college students, non-medical use of prescription stimulants, self-report, substance related disorders

INTRODUCTION

Non-medical use (NMU) of prescription stimulant medications is a continuing public health concern (1–3). Emergency department (ED) visits related to NMU of stimulant medications increased 200% from 2005 to 2010 (4). Between 2006 and 2011, despite no change in treatment visits for adults involving prescriptions of dextroamphetamine, amphetamine or methylphenidate, NMU of prescription stimulants increased 67% and ED visits increased 156% (5). College students are particularly likely to engage in NMU of prescription stimulants (5–10). Past-year NMU of prescription stimulants is more common among 18–25 year-olds (∼7.5%) compared with younger and older age groups (both ≤ 2%) (11).

Stimulant medications prescribed for attention-deficit/hyperactivity disorder (ADHD) are widely available on college campuses (12). One longitudinal study (13, 14) followed a single cohort of college freshmen for 4 years. Over the follow-up period, nearly two-thirds were offered prescription stimulants for NMU and 31% reported NMU, a prevalence echoed by other surveys (15).

One motivation for stimulant NMU is enhanced academic performance (1, 16), despite evidence that stimulant NMU does not improve academic performance (7, 10, 17). Stimulant NMU is associated with other drug use and/or heavy drinking (18, 19).

While most stimulant NMU is by oral routes, non-oral NMU has been noted (6, 14, 20). Only a few studies of college students have evaluated non-oral ROAs of prescription stimulants (14, 20), usually snorting and less often injection and smoking (7, 21). Drugs taken via injection, smoking and snorting have a more rapid onset than oral ingestion, resulting in greater reinforcement for getting high and addictive potential (22). Non-oral routes also enhance the risk of cardiovascular failure, cardiac arrhythmia, high blood pressure, paranoia (10) as well as hospitalization and death (23). Levels of prescription stimulant smoking or injection (when reported) in the general population of adults (6) and among college students (20) have been low (< 6%). Estimates of snorting by college students range from 17% (14) to ∼40% (20, 21).

The Food and Drug Administration (FDA) has declared NMU of prescription stimulants a serious public health concern and has called for the assessment of the potential impact of abuse deterrent formulations (ADFs) for prescription stimulants (24). ADFs, designed to deter non-oral use, have demonstrated benefits in reducing abuse of prescription drugs and associated adverse consequences, especially for prescription opioids (25–27). Examination of non-oral ROAs of prescription stimulants by college students has been previously identified as useful for determining the potential value of abuse deterrent formulations (ADFs) (16, 19). Surprisingly, little research has considered the characteristics or practices of college students who use non-oral ROAs.

One such characteristic is polydrug use, which is the misuse of more than one class of psychoactive prescription drugs (28). Toward this end we examined prescription stimulant NMU in the context of polydrug use by college students. We sought to investigate, descriptively, pathways of non-medical use and abuse of other non-alcohol substances. This may be particularly important given that initial exposure to prescription stimulants may occur via legitimate treatment for ADHD symptoms, as opposed to the traditional "gateway hypothesis" (29) which posits that early experimentation with alcohol, tobacco or marijuana is associated in a causal way to increased substance involvement later in life.

The present cross-sectional study used a self-report, online survey to characterize a sample of college students reporting NMU of prescription stimulants to gain a preliminary view of respondents' routes of administration, factors contributing to the NMU, and pathways of initiation associated with specific patterns of non-oral use. We particularly sought to consider whether prescription stimulant NMU by college students is the only type of misuse/abuse of non-alcohol substances, is an initial foray into misuse/abuse of other substances or occurs within the context of ongoing polysubstance abuse. Finally, we sought to examine the associations among different ROAs, motivations for NMU and sources of procurement of the prescription stimulants being misused.

METHODS

Definition of Non-medical Use and Non-oral Use

Following the convention employed by the National Survey on Drug Use and Health (NSDUH) (30), medication NMU was defined as meeting at least one of three criteria within the respondents' lifetime: (1) use for any reason, even once, without one's own prescription; (2) use in ways other than

prescribed, such as taking more than prescribed or more often than prescribed; and (3) use for the feeling or experience that the medication caused, such as feeling high, enhancement of other drugs, or prevention or treatment of withdrawal symptoms or other feelings. Non-oral use was defined as use by smoking, snorting and/or injection (31). Oral use included swallowing whole, chewing, and dissolving in liquid then swallowing.

Study Population

An online survey of college students was conducted using an opt-in panel operated by YouGov®, an Internet-based market research and data analytics firm. The sample was created by YouGov from a pool of 3,379 respondents, who were matched to a sampling frame constructed from the 18–26-year-old, college student sample of the 2016 American Community Survey (ACS). The matched cases were weighted to the sampling frame using propensity scores based on age, gender, race/ethnicity, years of education, and region. The current study includes a subsample of 486 respondents who met inclusion criteria (age 18–26 years, currently enrolled in college, and reported prescription stimulant NMU at any time in their lifetime).

Participants are not paid to join the YouGov panel but receive points for completing surveys that can be redeemed for cash or charitable contributions. All participants provided electronic informed consent, however, respondents remained anonymous to the researchers. The consent form and study received approval by the New England Institutional Review Board (NEIRB).

Questionnaire

The author-constructed survey took <15 min to complete. Respondents provided demographic information, college characteristics, and medical history, including self-report of lifetime substance use disorder (SUD) and psychiatric diagnoses. All participants reported lifetime prescription stimulant NMU and were asked about the time frame of use, motivations for NMU, sources of medication procurement, and ROA. The survey was limited to Schedule II pharmaceutical products that are FDA approved for ADHD and are in tablet or capsule form intended for oral administration. Other products or compounds, such as the methylphenidate analogs (32), were not included as part of the survey. Respondents were asked about lifetime NMU of prescription opioids, binge alcohol use in the past 30 days (five or more drinks in a single occasion), lifetime marijuana use, and lifetime "illegal drug" use, including cocaine/crack, heroin, street fentanyl, inhalants, amphetamines/methamphetamines, hallucinogens, sedatives, or other illegal substances. Students estimated their age at first NMU of prescription drugs, marijuana, and illegal drugs, in order to calculate drug initiation pathways of prescription stimulant NMU for polysubstance users.

Statistical Analysis

Sample characteristics are presented as frequencies and proportions. Self-reported pathways of initiation of prescription stimulant NMU are presented descriptively based on retrospective answers to the age-at-first-use question. Univariate pairwise comparisons of ROA subgroups (oral-only, snorting with no injection, and injection) used chi-square tests, Fisher's exact tests, or *t*-tests as appropriate.

Logistic regression models evaluated factors associated with non-oral vs. oral-only prescription stimulant NMU, including: age; sex; race; diagnoses of ADHD, lifetime psychiatric disorder (depression, anxiety or bipolar disorder), alcohol or substance use disorder, or conduct or oppositional defiant disorder; binge alcohol use in the past 30 days; lifetime marijuana use, lifetime use of cocaine, heroin, or illegal stimulant, and lifetime NMU of prescription opioids. Findings are presented as odds ratios (OR) and 95% confidence intervals (CI).

Statistical analyses were conducted using Statistical Analysis Software (SAS) Enterprise Guide Version 7.1 (SAS Institute, Cary, NC). For logistic regression models, *p*-values were two-sided and considered significant at p-values < 0.05. To explore correlates associated with various ROAs employed by participants, we conducted a high number of pairwise comparisons. Bonferroni adjusted *p*-values were used for analyses of medication procurement and motivation ($p < 0.006$). Exploratory analyses of factors associated with different ROA use employed an adjusted *p*-value of 0.003. Otherwise, *p*-values $<$ 0.05 are presented in the tables.

RESULTS

Survey Sample Characteristics

Among the 486 college students reporting lifetime prescription stimulant NMU, 59.9% were women; most were white, single, and full-time undergraduates from public schools (**Table 1**). Colleges were in the South (39.9%), Midwest (21.4%), West (20.8%) and Northeast (17.9%). Two-hundred-ten students (43.2%) reported a lifetime diagnosis of ADHD, of which 70% were diagnosed at age 16 or older. More than three-quarters (77.6%) reported a lifetime psychiatric diagnosis (depression, anxiety, or bipolar disorder), while 29.6% reported a lifetime alcohol or substance use disorder. Binge alcohol use in the past 30 days was reported by 12%, while lifetime use of cocaine, heroin and illicit stimulants ranged from 15.8% for heroin to 35.4% for cocaine. Lifetime NMU of prescription opioid medication was 58.6%, and marijuana use was reported by 73.7%.

Factors Associated With Use by Non-oral Routes

For the logistic regression and ROA analyses, 99.2% of all respondents ($n = 482$) were included in the analyses (four were excluded due to missing data). Among college students reporting prescription stimulant NMU included in the logistic regression analyses, 23.2% ($n = 112$) reported at least one non-oral ROA. Univariate results of the logistic regression (**Table 2**) identified factors associated with non-oral ROAs, including male gender (OR: 0.49, 95% CI: 0.32–0.076), lifetime diagnoses of alcohol or other substance use disorder (OR: 3.14, 95% CI: 2.02–4.88), conduct/oppositional defiant disorder (OR: 3.65, 95% CI: 2.32–5.74), and lifetime use of illegal drugs (i.e., cocaine, heroin or illegal stimulants; OR: 2.40, 95% CI:1.56–3.69). A lifetime diagnosis of ADHD (OR: 1.92, 95% CI: 1.26–2.95) and a history of NMU of prescription opioids (OR: 1.85, 95% CI:

TABLE 1 | Characteristics of college students by lifetime non-medical use of prescription stimulants.

Characteristic	Total sample (*N* = 486) No. (%)
Sex	
Male	195 (40.1)
Female	291 (59.9)
Age, years	
18–20	162 (33.3)
21–23	196 (40.3)
24–26	128 (26.3)
Race	
White	319 (65.6)
Black	54 (11.1)
Hispanic/Latino	47 (9.7)
Asian	41 (8.4)
Native American	4 (0.8)
Middle Eastern	6 (1.2)
Other	2 (0.4)
Mixed race	13 (2.7)
Marital status	
Married/living with spouse	81 (16.7)
Separated	7 (1.4)
Divorced	4 (0.8)
Widowed	1 (0.2)
Single/never married	365 (75.1)
Domestic partnership	28 (5.8)
Year of college	
Undergraduate/community college	358 (73.7)
Graduate	128 (26.3)
Type of student	
Full-time	370 (76.1)
Part-time	116 (23.9)
Type of college	
Public	378 (77.8)
Private	108 (22.2)
US Region for the college	
Northeast Region	87 (17.9)
Midwest Region	104 (21.4)
South Region	194 (39.9)
West Region	101 (20.8)
Lifetime diagnosis of ADHD	210 (43.2)
Lifetime diagnosis of psychiatric disorder (depression, anxiety, or bipolar disorder)	377 (77.6)
Lifetime diagnosis of alcohol or substance use disorder	144 (29.6)
Lifetime diagnosis of conduct or oppositional defiant disorder	124 (25.5)
Binge alcohol use in past 30 days[a]	59 (12.1)
Marijuana use in lifetime	358 (73.7)
Cocaine use in lifetime	172 (35.4)
Heroin use in lifetime	77 (15.8)
Illicit stimulant use in lifetime	134 (27.6)
Non-medical use of prescription opioids in lifetime	285 (58.6)

NMU, nonmedical use.

[a]*Binge drinking defined as consuming five or more drinks in a single occasion.*

1.18–2.90) were also significantly associated with use by a non-oral ROA, albeit to a lesser degree. Multivariable analyses yielded significant adjusted ORs for only two factors: lifetime diagnosis of conduct/oppositional defiant disorder (adjusted OR: 2.27, 95% CI: 1.15–4.48) and lifetime use of illicit drugs (adjusted OR: 1.99, 95% CI: 1.18–3.37) (**Table 2**), implying a relatively high concordance between many of the various factors investigated (r_s among the significant variables in the univariate analysis ranged from 0.17 to 0.66, all $p < 0.001$) (33).

Non-oral ROAs Reported

While most of the 486 college students reported NMU of stimulants via oral routes (92.0%), 23.0% reported any non-oral use: snorting (20.4%), smoking (6.0%) and/or injection (3.5%). Among those reporting non-oral NMU of prescription stimulants, two-thirds (66.1%) also reported oral NMU. Among the 112 non-oral users, 88.4% reported snorting, 25.9% reported smoking, and 15.2% reported injecting. Since individuals often report more than one ROA, percentages do not add to 100%.

Source of Procurement for Prescription Stimulants

Overall, most respondents (67.3%) reported obtaining the medication from a family member or friend, followed by their own prescription (39.7%). **Table 3** (top) presents comparisons of drug source in respondents who use oral routes only with those who snort but do not inject, and those who inject. Respondents reporting injecting and/or snorting were more likely than oral-only respondents to obtain their drug from a dealer, to have bought online without a prescription, or to have faked a prescription ($p < 0.001$). Report of injection was more often than oral-only use to be associated with stealing the drug ($p = 0.004$). Those who reported snorting were more likely than oral-only users to have traded for the drug ($p = 0.001$). Significant differences were not found for snorting only vs. injection.

Motivations for NMU of Prescription Stimulants

Nearly half (47.7%) of all respondents listed enhancing work or school performance as a motivation for prescription stimulant NMU, 23.3% for increased energy, and 14.6% for getting high or enhancing the effect of other drugs. Comparisons across ROA patterns (**Table 3** lower) revealed that those who snort and/or inject were more likely than oral-only users to report getting high, enhancing the effect of other drugs, and controlling appetite as motivations for NMU. Those injecting were more likely than oral-only users to report motivation for energy, to treat withdrawal symptoms, and to report using the drug by mistake (i.e., "forgot they already took it").

Factors Associated With Prescription Stimulant NMU Route of Administration

Oral ROA was reported by 92.0% of respondents: 83.4% swallowed whole, 14.8% by chewing, and 18.3% dissolved in liquid to drink. Non-oral NMU was observed in 23.0% of all respondents. Within each group, 20.4% of the whole sample and 88.4% of the non-oral sample reported snorting; 6.0% of the

TABLE 2 | Factors associated with lifetime non-medical use of prescription stimulants via non-oral routes* compared with oral routes only among college students ($N = 482$**).

	Lifetime NMU of Rx stimulants via non-oral routes ($N = 112$)		
	No./Total (%)	**Univariate-unadjusted OR (95% CI) *p*-value**	**Multivariable-adjusted OR (95% CI) *p*-value**
Age, years			
18–20	31/162 (19.1)	0.65 (0.38–1.14)	0.86 (0.47–1.58)
21–23	47/192 (24.5)	0.90 (0.54–1.50)	1.01 (0.58–1.74)
24–26	34/128 (26.6)	Ref	Ref
		NS	NS
Sex			
Female	52/288 (18.1)	0.49 (0.32–0.76)	0.65 (0.40–1.04)
Male	60/194 (30.9)	Ref	Ref
		$p = 0.0012$	NS
Race/ethnicity			
White	72/317 (22.7)	0.92 (0.59–1.43)	1.00 (0.62–1.62)
Non–white	40/165 (24.2)	Ref	Ref
		NS	NS
Lifetime diagnosis of ADHD			
Yes	62/207 (30.0)	1.92 (1.26–2.95)	1.02 (0.58–1.79)
No	50/275 (18.2)	Ref	Ref
		$p = 0.003$	NS
Lifetime diagnosis of psychiatric disorder (depression, anxiety, or bipolar disorder)			
Yes	94/374 (25.1)	1.68 (0.96–2.93)	1.13 (0.60–2.13)
No	18/108 (16.7)	Ref	Ref
		NS	NS
Lifetime diagnosis of alcohol or substance use disorder			
Yes	55/142 (38.7)	3.14 (2.02–4.88)	1.30 (0.66–2.55)
No	57/340 (16.8)	Ref	Ref
		$p < 0.001$	NS
Lifetime diagnosis of conduct or oppositional defiant disorder			
Yes	52/123 (42.3)	3.65 (2.32–5.74)	2.27 (1.15–4.48)
No	60/359 (16.7)	Ref	Ref
		$p < 0.001$	$p = 0.019$
Binge alcohol use in past 30 days			
Yes	16/58 (27.6)	1.30 (0.70–2.42)	1.48 (0.75–2.92)
No	96/424 (22.6)	Ref	Ref
		NS	NS
Marijuana use in lifetime			
Yes	81/355 (22.8)	0.92 (0.57–1.47)	0.90 (0.50–1.61)
No	31/127 (24.4)	Ref	Ref
		NS	NS
Other illicit drug (cocaine, heroin, or illegal stimulant use) in lifetime			
Yes	63/192 (32.8)	2.40 (1.56–3.69)	1.99 (1.18–3.37)
No	49/290 (16.9)	Ref	Ref
		$p < 0.001$	$p < 0.010$
Non-medical use of prescription opioids in lifetime			
Yes	78/283 (27.6)	1.85 (1.18–2.90)	1.09 (0.65–1.81)
No	34/199 (17.1)	Ref	Ref
		$p = 0.008$	NS

CI, confidence interval; NMU, nonmedical use; OR, odds ratio; Ref, reference; Rx, prescription.

**Non-oral routes include snorting, smoking, and/or injection. Oral routes include swallowing whole, chewing in mouth then swallowing, and/or dissolving in liquid then swallowing.*

***Four respondents were excluded from the model due to missing data.*

TABLE 3 | Source of procurement and motivations for NMU of prescription stimulants by route.

	Oral-only *N* = 370	Snorting no injection *N* = 88*	Injection *N* = 17	Oral-only vs. Snorting no injection**	Oral-only vs. injection**	Injection vs. Snorting no injection**
Number and percent¥ indicating source of procurement of prescription stimulant by route						
Bought/given/stole it from family or friend	239 (64.6%)	70 (79.5%)	10 (58.8%)	0.008	NS	NS
My own prescription from one doctor or several doctors	146 (39.5%)	33 (37.5%)	11 (64.7%)	NS	0.045	NS
Bought it from a dealer	29 (7.8%)	26 (29.6%)	8 (47.1%)	<0.001	<0.001	NS
Bought it online without a doctor's visit	24 (6.5%)	19 (21.6%)	8 (47.1%)	<0.001	<0.001	0.037
Traded for it	11 (3.0%)	11 (12.5%)	2 (11.8%)	0.001	NS	NS
Wrote or bought a fake prescription	4 (1.1%)	9 (10.2%)	5 (29.4%)	<0.001	<0.001	0.049
Stole them from someone I did not know	5 (1.4%)	5 (5.7%)	3 (17.6%)	0.026	0.004	NS
"Other" source	2 (0.5%)	0 (0.0%)	0 (0.0%)	NS	NS	NS
Number and percent¥ motivations for NMU of prescription stimulants by route						
To enhance performance at work or school	189 (51.1%)	36 (40.9%)	4 (23.5%)	NS	0.044	NS
For energy	76 (20.5%)	25 (28.4%)	9 (52.9%)	NS	0.004	NS
To treat ADHD	69 (18.6%)	9 (10.2%)	4 (23.5%)	NS	NS	NS
To improve my mood or elevate my spirit	52 (14.1%)	20 (22.7%)	7 (41.2%)	NS	0.008	NS
To get high/enhance effect of other drugs	32 (8.6%)	28 (31.8%)	9 (52.9%)	<0.001	<0.001	NS
To control appetite or for weight loss	21 (5.7%)	17 (19.3%)	6 (35.3%)	<0.001	<0.001	NS
To prevent or treat withdrawal symptoms	7 (1.9%)	4 (4.5%)	4 (23.5%)	NS	0.001	0.023
By mistake (such as forgot you already took it)	7 (1.9%)	4 (4.5%)	4 (23.5%)	NS	0.001	0.023
Other	6 (1.6%)	2 (2.3%)	0 (0%)	NS	NS	NS

¥ *Respondents select all that apply, so percentages do not add to 100%.*

**Seven individuals selected smoke and/or "other route" but not snorting or injection.*

***Difference between groups: bivariate comparisons used χ^2 and Fisher's Exact Test where appropriate. All p-values are 2-tailed.*

whole sample and 25.9% of the non-oral group smoked. Injection was reported by 3.5% of the whole group and 15.2% of the non-oral NMU respondents.

Comparing characteristics of individuals who use oral routes only with those who snort but do not inject and those who inject are presented in **Table 4**. Compared with respondents reporting oral routes only, college students who reported injecting stimulants were more likely to be men, to be a member of a Greek organization, to have an ADHD diagnosis, to have a lifetime substance use diagnosis, and to have a history of NMU of prescription opioids. Those who injected were more likely than the oral-only group and the snorting/no injection group to report use of heroin, sedatives, and street fentanyl. Snorting/no injection respondents more often reported a substance use diagnosis and use of cocaine/crack than those reporting oral ROA only.

Pathways of Initiation

Most respondents (n = 444, 91.4%) reported non-alcohol polysubstance use. Seventeen percent (n = 76) of the polysubstance users started prescription stimulant NMU at an age earlier than any of the other drugs endorsed. Another 12.2% (n = 54) first engaged in prescription stimulant NMU at the same age as at least one of the other drug categories. While the majority of those reporting polysubstance use also reported abusing other drugs before prescription stimulant NMU, 27.9% either initiated prescription stimulant NMU first or initiated polysubstance use concurrently with prescription stimulant NMU.

Table 5 presents an overview of the three sequences of misuse/abuse of prescription stimulants and other drugs for all polysubstance users and by ROA - i.e., prior to, coincident with, or following first NMU of prescription stimulants. Nearly two-thirds (64.2%) of all polysubstance users reported NMU of prescription opioids, of whom 38.6% initiated prescription opioid NMU prior to NMU of prescription stimulants, 16.1% initiated NMU of these medications at the same age, and 45.3% started NMU of prescription stimulants first. Among those who used illicit drugs other than marijuana (55.0% of all polysubstance users), 43.3% used such drugs prior to prescription stimulants, 24.6% at the same age, and 32.0% started NMU of prescription stimulants prior to using illicit drugs.

Lifetime marijuana use was reported by 80.6% of all polysubstance users, and 56.1% reported using marijuana or marijuana plus another substance prior to initiating prescription stimulant NMU. Among all marijuana users, ∼70% reported using marijuana prior to prescription stimulant NMU, while nearly 20% reported NMU of prescription stimulants prior to marijuana use. Nearly 1 in 5 (18.7%) of all polysubstance users reported marijuana use and prescription stimulant NMU only, while 14.6% used marijuana prior to prescription stimulant NMU, 3.2% reported initiating prescription stimulant NMU prior to marijuana, and 0.9% initiated use of both substances at the same age.

The breakdown of the drug-use sequences in **Table 5** by ROA pattern revealed no significant differences between those who report NMU of prescription stimulants orally only, those

TABLE 4 | Exploratory factors associated with ROA patterns reported for prescription stimulants.

	Oral-only $N = 370$	Snorting no injection $N = 88$*	Injection $N = 17$	Oral-only vs. Snorting no injection**	Oral-only vs. injection**	Injection vs. Snorting no injection**
Age, mean (SD)	21.7 (2.5)	22.0 (2.5)	22.2 (2.2)	NS	NS	NS
Race (White), No. (%)	245 (66.2)	60 (68.2)	10 (58.8)	NS	NS	NS
Gender (M), No. (%)	134 (36.2)	42 (47.7)	13 (76.5)	NS	<0.001	0.04
Member fraternity or sorority, No. (%)	100 (27.0)	33 (37.5)	11 (64.7)	NS	0.002	NS
Lifetime psychiatric, No. (%)	280 (75.7)	71 (80.7)	17 (100.0)	NS	0.02	NS
ADHD diagnosis, No. (%)	145 (39.2)	43 (48.9)	13 (76.5)	NS	0.002	NS
Substance use diagnosis, No. (%)	87 (23.5)	34 (38.6)	15 (88.2)	<0.001	<0.001	<0.001
Past 30-day Rx stimulant NMU, No. (%)	159 (43.0)	44 (50.0)	11 (64.7)	NS	NS	NS
NMU of prescription opioids, No. (%)	205 (55.4)	56 (63.6)	16 (94.1)	NS	0.002	0.01
Marijuana, No. (%)	274 (74.1)	66 (75.0)	11 (64.7)	NS	NS	NS
Cocaine or crack, No. (%)	109 (29.5)	48 (54.5)	10 (58.8)	<0.001	0.01	NS
Illicit amphetamines/methamphetamine, No. (%)	89 (24.1)	31 (35.2)	9 (52.9)	0.04	0.02	NS
Hallucinogens, No. (%)	117 (31.6)	40 (45.5)	10 (58.8)	0.02	0.02	NS
Heroin, No. (%)	49 (13.2)	15 (17.0)	9 (52.9)	NS	<0.001	0.003
Street fentanyl, No. (%)	39 (10.5)	11 (12.5)	10 (58.8)	NS	<0.001	<0.001
Inhalants, No. (%)	65 (17.6)	21 (23.9)	9 (52.9)	NS	0.001	0.02
Sedatives, No. (%)	49 (13.2)	17 (19.3)	10 (58.8)	NS	<0.001	0.002
Other illicit substance, No. (%)	45 (12.2)	15 (17.0)	6 (35.3)	NS	0.02	NS

Note: Seven individuals selected smoke and/or "other route" but not snorting or injection.

***Difference between groups: bivariate comparisons used χ^2 and Fisher's Exact Test where appropriate. All p-values are 2-tailed.*

who snort but do not inject, and those who inject. While the percentages of those who used illicit drugs other than marijuana prior to NMU of prescription stimulants were much greater for those who inject (i.e., 45.0% for oral-only and 33.3% for snort/no inject vs. 72.7% for those who inject), these differences did not reach statistical significance.

DISCUSSION

This cross-sectional, online survey evaluated prescription stimulant NMU among college students in the United States. Pathways of initiation of prescription stimulant NMU were presented, as well as characteristics of non-oral use.

All respondents to this survey engaged in NMU of stimulants, while nearly one in four (23%) reported non-oral use. Non-oral use was consistently associated with increased likelihood of serious, non-alcohol substance use. Although other studies have found ADHD diagnosis, gender, race, depression, anxiety, marijuana and alcohol use to be associated with prescription stimulant NMU (34), in this study age, race, recent alcohol binge drinking, and marijuana use did not differentiate oral and non-oral NMU. Univariate analyses revealed associations of major factors with reports of non-oral ROA, especially being male, lifetime diagnoses of ADHD, alcohol or other substance disorder as well as conduct/oppositional defiant disorder, and history of prescription opioid NMU.

The finding that women students were less likely overall to report non-oral NMU practices, may be an underlying feature common to many of the other factors investigated. For instance, women are less likely to be diagnosed with ADHD and, women diagnosed with ADHD appear to exhibit lower levels of conduct problems than their male counterparts (35), both factors that were associated with non-oral ROA NMU in this survey. Women were significantly less likely to inject, even if they reported snorting prescription stimulants, however, oral-only ROA vs. snorting but not injection were not significantly different by gender. Injecting may be associated with higher risk-taking behavior in men with ADHD (35). On the other hand, other studies of gender differences in adults with ADHD (36) have found women with an ADHD diagnosis to be much more likely than women without one to express suicidal ideation, which may be a very different phenomenon than male risk-taking behavior.

Of those reporting non-oral prescription stimulant NMU, the large majority (88%) snorted the medication, with a quarter reporting smoking and 15% injecting. Our findings are consistent with those from the few studies investigating injection of prescription stimulants, suggesting that injection of these medications is relatively rare (6, 20, 23). Because the small number of college students who inject prescription stimulants in this sample resulted in point estimates that may not be stable, the findings reported for non-oral injection users should be considered preliminary and used to stimulate further research. However, even though injection may be rare, it is associated with much higher risk and understanding what motivates this behavior may inform prevention and treatment strategies.

Compared with oral-only users, respondents reporting any non-oral route were more likely to have more serious substance use histories and drug-use patterns. Non-oral use is consistently

TABLE 5 | Pathways of multi-drug use that involved prescription stimulant NMU[¥] for all respondents and by ROA.

Polysubstance users[¥]	Total $N = 444$		Oral-only $N = 370$		Snorting no injection $N = 88$*		Injection $N = 17$		Oral-only vs. Snorting no injection**		Oral-only vs. injection**		Injection vs. Snorting no injection**	
	n	Col %	*n*	Col %	*n*	Col %	*n*	Col %	*p*-value		*p*-value		*p*-value	
Prescription opioids	**285**	**100.0**	**205**	**100.0**	**56**	**100.0**	**16**	**100.0**						
Before stimulants	110	38.6	73	35.6	25	44.6	8	50.0	NS		NS		NS	
Same age stimulants	46	16.1	34	16.6	9	16.1	2	12.5						
After stimulants	129	45.3	98	47.8	22	39.3	6	37.5						
Marijuana	**358**	**100.0**	**274**	**100.0**	**66**	**100.0**	**11**	**100.0**						
Before stimulants	249	69.6	194	70.8	42	63.6	9	81.8	0.0489		NS		NS	
Same age stimulants	38	10.6	24	8.8	13	19.7	0	0.0						
After stimulants	71	19.8	56	20.4	11	16.7	2	18.2						
Illicit drugs (other than marijuana)[€]	**244**	**100.0**	**171**	**100.0**	**57**	**100.0**	**11**	**100.0**						
Before stimulants	106	43.4	77	45.0	19	33.3	8	72.7	NS		NS		NS	
Same age stimulants	60	24.6	40	23.4	18	31.6	1	9.1						
After stimulants	78	32.0	54	31.6	20	35.1	2	18.2						

[¥] Respondents reporting lifetime use of at least 1 of the following in addition to lifetime prescription stimulant NMU: prescription opioids, marijuana, or other illicit drugs (other than marijuana).

[€] Includes cocaine, heroin, street fentanyl, inhalants, illicit amphetamines, hallucinogens, barbiturates, and 'other' illicit substances.

**Seven individuals selected smoke and/or "other route" but not snorting or injection.*

***Difference between groups: bivariate comparisons used χ^2 and Fisher's Exact Test where appropriate. All p-values are 2-tailed.*

associated with serious adverse consequences (10), increased prevalence of overdose (37), addictive potential (38) and significant risk of morbidity and mortality (23). Note that in the current study, the large majority of those who reported NMU of prescription stimulants via non-oral routes snorted the drug. Further research into this type of non-oral prescription stimulant NMU is warranted, as such work may clarify a role that ADF formulations can have in reducing the serious adverse consequences of non-oral prescription stimulant NMU (16, 19, 23, 24).

Consistent with findings of earlier research (7, 10, 39), two-thirds of NMU respondents obtained the prescription stimulant from a family member or friend (either bought, given, or stolen). About 40% obtained the stimulant through a legitimate prescription. Non-oral users, on the other hand, endorsed other sources, especially getting the drug from a "dealer," and online purchases, while also obtaining prescription stimulants through the usual sources of friends, family, and providers.

The motivation most often reported for NMU by oral routes and snorting was performance enhancement, as others have noted (3, 7, 10, 40). Such oral NMU of prescription stimulants for performance enhancement may signal the lack of adequate resources or supports for students in a highly artificial (e.g., memory-based performance testing), high stress environment, where academic outcomes can have life-altering consequences. NMU for performance enhancement by students with ADHD using oral routes also raises questions regarding the perceptions by these patients as to the adequacy of their treatment (16). It may also be relevant that learning problems often associated with an ADHD diagnosis may be more responsive to treatments other than medication (35). Although not among the most often reported motivations by those who inject, performance enhancement was reported as a motivation for NMU by nearly a quarter of those respondents. Those reporting snorting and injection were significantly more likely than the oral-only group to report motivations to get high or to enhance the effects of other drugs. These motivations and the higher likelihood of polysubstance use in non-oral users are indicative of higher risk behaviors often associated with having or developing significant substance use problems.

More than 90% of prescription stimulant NMU was observed in the context of polysubstance use (not including alcohol); a finding consistent with results of a population-based survey (41). Among polysubstance users, 18.7% reported marijuana as the only other drug used. While 80.6% of polysubstance users reported marijuana use, and 69.6% of those reported marijuana use prior to prescription stimulant NMU, marijuana was considered separately in this study, given its legal status in many states for use by at least some individuals in the examined age range as well as changing views of marijuana use by the public (42, 43). Nevertheless, it is noteworthy that prescription stimulant NMU preceded prescription opioid NMU 45% of the time and preceded illegal drug use 32% of the time. Our pathways analyses are conceptually similar to the so-called "gateway hypothesis" (29), which proposes that a child or adolescent's early experimentation with or exposure to alcohol, tobacco, or cannabis leads to more addictive illicit drugs later

in adulthood (44, 45). Empirical examination of the gateway hypothesis has yielded conflicting and ambiguous results (45, 46), suggesting that a simple, causal role of early exposure to abusable or addictive substances is unlikely. Interpretation of early prescription stimulant NMU in the pathway toward use of illegal drugs, NMU of other prescription drugs or use by non-oral routes is complex. There is evidence from this survey and other research (47) that an ADHD diagnosis maybe a risk factor for later serious drug involvement (i.e., polysubstance use and non-oral ROA use). Specifically investigating exposure to ADHD medications in childhood and adolescence, McCabe et al. (48) found that children who initiated stimulant medication for ADHD early (aged 9 or less) and for longer duration (6 or more years) did not differ between population controls (youth without ADHD and unmedicated youth with ADHD).

The pathway findings among the 90% of survey respondents reporting polydrug use in this study support other studies that suggest primary care physicians largely underestimate the potential for NMU and diversion of ADHD medications by their patients (16). Thus, the findings presented here suggest that prescription stimulant NMU coincided with a more general pattern of substance misuse/abuse. Prescribers should at least be cognizant of the potential for current or later escalation of substance use by their patients. This study shares the limitations of other online surveys, including self-selection bias, self-report of drug use and medical diagnoses, and the use of an online panel. Although efforts were made to establish a representative sampling frame from which to draw respondents, the final sample may not be representative of college students who engage in NMU. While many of the findings are consistent with those from other studies, generalization should be approached cautiously. Use of a cross-sectional survey to explore retrospective recall of pathways of drug initiation across time is, by definition, limited, and can only be considered suggestive. In agreement with other authors (9), our use of the Internet panel survey is intended to complement, not replace, national probability studies.

CONCLUSIONS

A number of authors have proposed policies and interventions to address college student prescription NMU that are often educational in nature, stressing legal and ethical concerns (i.e., is NMU "cheating?") and combating the "misinformation" that prescription stimulant NMU is harmless (10). Over-estimation of the extent to which stimulant products enhance memory, attention and creativity for individuals outside the treatment of ADHD (49) may have important implications for educational interventions. Identifying and providing services to those at risk for mental health and substance use issues has also been proposed (10). A comprehensive strategic planning guide has recently been published online by the Drug Enforcement Administration (50) to address prescription stimulant NMU. The guide covers assessment, building capacity and programs, implementation, and evaluating the impact of interventions. Some authors have stressed viewing NMU as a "red flag" for possible involvement in other illicit drug use, poor academic performance, and mental health problems (18, 19) and called for better diagnostic practices for ADHD (7), which can present challenges in adults (51, 52).

Our finding that nearly a quarter of NMU involved non-oral routes highlights the importance of non-oral NMU of prescription stimulants. This concerning rate of non-oral NMU suggests that further work should explore methods to reduce such use and the deleterious outcomes associated with snorting or injecting the drugs. Promising efforts to reduce the prevalence and negative impacts of prescription stimulant NMU among college students likely include a range of preventive approaches addressing policy, education, diagnostic practices and detection of malingering, paired with treatment approaches utilizing cognitive behavior therapy (53, 54), interventions geared to patients' specific needs, such as personality-targeted interventions (55), sensitivity to the unique needs of women with ADHD, who, for instance, appear to be more impacted by parenting style (56) than male ADHD patients, use of therapies other than medications when learning problems are a major presenting complaint (35), and, possibly, medication formulations that present barriers to non-oral use (16, 19, 23, 24).

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 New England Institutional Review Board (NEIRB). The patients/participants provided electronic informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB, SF, AR, JN, KA, and JG contributed to conception and design of the study. SB and RR performed the statistical analysis. SB wrote the first draft of the manuscript. SF, AR, JN, and JG wrote sections of the manuscript and provided specific edits/revisions. All authors contributed to the article and approved the submitted version.

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An Examination of Risk Factors for Tobacco and Cannabis Smoke Exposure in Adolescents Using an Epigenetic Biomarker

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Objective: Evolving patterns of nicotine and cannabis use by adolescents require new tools to understand the changing epidemiology of these substances. Here we describe the use of a novel epigenetic biomarker sensitive to both tobacco and cannabis smoke in a longitudinal sample of high-risk adolescents. We examine risk factors for positivity for this epigenetic biomarker in comparison to positivity for conventional serum biomarkers of nicotine and cannabis use.

Method: Eastern Iowa 10th graders who had a friend or family member who smoked were eligible to participate in a longitudinal study over 10–12th grades. Subjects provided self-report data on nicotine, tobacco, and cannabis use patterns as well as blood samples that were used for serum cotinine and THC assays. DNA was prepared for analysis of methylation at the CpG cg05575921, a sensitive indicator of smoke exposure. Relationships between positivity for each these biomarkers and a variety of risk factors, including demographics, family and peer relationships, psychopathology, willingness to smoke, and perceptions of typical cigarette and cannabis users, were examined at the 10th ($n = 442$), 11th ($n = 376$), and 12th ($n = 366$) grade timepoints.

Results: A increasing proportion of subjects were positive for cotinine (5–16%), THC (3–10%), and cg05575921 methylation (5–7%) across timepoints, with some overlap. Self-reported combusted tobacco and cannabis use was strongly correlated with all biomarkers, whereas cg05575921 methylation was not correlated with reported e-cigarette use. Dual users, defined as those positive for nicotine and THC in the 12th grade showed the greatest cumulative smoke exposure, indicated by cg05575921 methylation. Subjects reported more positive attitudes toward cannabis users than cigarette smokers, and willingness to smoke and positive perceptions of tobacco and cannabis smokers were significant risk factors for biomarker positivity across timepoints.

Conclusion: We conclude that measurement of cg05575921 methylation in adolescents is a useful tool in detecting tobacco smoking in adolescents, and may be a novel tool for the detection of cannabis smoking and cannabis and tobacco co-use, though non-combusted forms of nicotine use do not appear to be detectable by this method.

Keywords: smoking, epigenetics, DNA methylation, AHRR, cg05575921, digital PCR, adolescent

INTRODUCTION

The landscape of adolescent smoking has seen significant changes over the past three decades. Since 1991, past 30-day cigarette use by 18-year-olds in the US has declined from 18.5% to under 5%, while the proportion disapproving of cigarette use increased from 70% to nearly 90%, and the proportion viewing smoking as having a "great" risk increased from 50 to 75% (1). Concurrently, while the proportion of 12th graders reporting regular cannabis use held steady at around 6%, the proportion disapproving of cannabis decreased from roughly 90 to 65%, and the proportion viewing regular cannabis use as risky decreased from nearly 80% to under 30%. Thus, while the decrease in adolescent smoking is rightly viewed as a public health success, increasingly positive perceptions of cannabis along with expanding legalization of cannabis use across the US (2) are concerning trends.

Tobacco and cannabis co-use, e.g., cannabis smoked in a tobacco cigar as a "blunt," is a trend that has also prompted significant concern, as co-use is associated with worse overall outcomes than either alone (3, 4). While this form of use has been shown to be particularly prevalent among African-American youth (5, 6), it remains poorly defined and understudied (7). Some studies report that blunt smokers perceive them to be more "natural," less addictive (8, 9), more socially acceptable (10, 11), and less risky than cigarettes (12). In fact, nicotine appears to heighten the reinforcing effects of cannabis (13), increasing the risk of subsequent addiction (14). Studies have also shown that cannabis users are more likely to go on to smoke cigarettes (15), while cigarette users are more likely to use cannabis (16).

Lastly, the rise of e-cigarette use by adolescents is an emerging public health crisis (17), with past 30-day use among 12 graders estimated at 25% by the Monitoring the Future study (18). E-cigarettes carry acute risks of lung injury in some users (19) and longer-term risks of progression to nicotine dependence and unintended transitioning to combusted tobacco use (20). E-cigarette use has also been linked to a higher risk of using vaporized cannabis products (21), which may in turn predispose to cannabis dependence and other risks.

In this rapidly evolving landscape, better tools are needed in order to monitor adolescent smoking patterns, both epidemiologically and clinically. Unfortunately, detecting adolescent substance use is not easy. The most commonly-used method, self-report, suffers from poor accuracy in adolescents, likely due to both stigma and illegality (22). For example, one study of 367 adolescents self-report of cannabis use status, determined by urinalysis, was only 64% sensitive (23), and another study reported that only two-thirds of youth with detectable serum cotinine admitted to smoking in the past 5 days (24). Reliability of self-report may be even lower in minorities (25), though in some cases self-reporting may be confounded by the fact that blunt smokers may not identify as "tobacco" users or be aware of their nicotine exposure (26).

Limitations of objective biomarkers of substance relate primarily to their short half-lives of detection (27). Exhaled carbon monoxide (CO), though easy to measure, is detectable for only 4–5 h and is insensitive to light smoking (28). Cotinine, the primary metabolite of nicotine, can be assayed in saliva, blood or urine, and has a longer half-life of 15–19 h but similarly lacks sensitivity in the sporadic smoking which is typical of adolescents (29); its metabolism may vary by ethnicity (30, 31). In addition, cotinine assays cannot distinguish the source of nicotine exposure, whether combusted cigarette, e-cigarette, or nicotine replacement therapy (NRT).

Recent advances in the field of epigenetics may offer a means of overcoming some limitations of current smoking biomarkers. In particular, multiple studies and meta-analyses (27, 32, 33) have shown that decreased methylation of the genomic CpG cg05575921, located in the gene *Aryl Hydrocarbon Receptor Repressor* (*AHRR*), is a strongly performing biomarker for cigarette (AUC = 0.99) (34) that is both sensitive to light smoking (35) and demonstrate dose-response characteristics (34, 36, 37).

Importantly, while demethylation of cg05575921 appears to be driven by exposure to polyaromatic hydrocarbons (PAHs) and other compounds of tobacco smoke, this mechanism does not appear to be specific to combusted tobacco alone (38–42). Both tobacco (43) and cannabis (44) smoke contain high levels of PAHs, which when inhaled increase expression of the *Aryl Hydrocarbon Receptor* (*AHR)*, and subsequently *CYP1A1* (45), facilitating detoxification of these compounds. Lastly, expression of *AHRR* increases as a regulatory response to increased AHR expression (40), which if unregulated may result in carcinogenesis (39).

In this study we explore the epidemiology of this novel epigenetic biomarker for smoke exposure in a longitudinal cohort of high-risk adolescents in Eastern Iowa. We examine a number of risk factors traditionally associated with tobacco and cannabis smoking including race (46) ethnicity (47), SES (48), parental education (48), parental supervision (3, 49), parental smoking (50), peer use (51, 52), significant other use (53), and both externalizing and internalizing psychopathology (54–57). We also examine two variables from the Prototype/Willingness Model of adolescent risk behavior that have been shown to predict non-intentional but volitional adolescent risk behaviors: perceptions of prototypical adolescent cigarette and cannabis

smokers (58), and willingness, an acknowledgment that under certain circumstances, one might engage in a risk behavior that was previously not intended or sought (59). Lastly, we examine the relationships between the conventional biomarkers of tobacco and cannabis smoking, serum cotinine and THC, and cg05575921 methylation, an epigenetic biomarker of smoke exposure.

Because measurable demethylation of cg05575921 reflects cumulative rather than short-term smoke exposure, we hypothesize that the number of significant risk factors for epigenetic positivity would increase over time. In addition, we hypothesize that co-users of tobacco and cannabis will demonstrate the greatest cumulative exposure to toxicants, as indicated by greater change in cg05575921 methylation.

MATERIALS AND METHODS

Subjects

Subjects were drawn from the Healthy Iowans Study, a longitudinal study of adolescents in Eastern Iowa focusing on nicotine use and related risk factors and risk behaviors. Study procedures and protocols were approved by the University of Iowa's Institutional Review Board (IRB ID # 201409705). To ensure confidentiality, a NIH Certificate of Confidentiality was obtained.

Recruitment procedures for the study have been previously described (60). In brief, subjects were sophomores attending one of seven Eastern Iowa high schools and were provided with information about the study through the school. Interested subjects were contacted by study staff who provided further information and completed enrollment along with their parent/guardian. A bilingual staff member was available for Spanish speaking participants or families. Prior to consent, each adolescent subject and their parent or guardian were informed that study procedures would include blood tests for the presence of nicotine and cannabinoid by-products, and that these would remain confidential and only be available to study staff in a de-identified form.

After consent, each subject was interviewed by a trained research assistant using an abbreviated child version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (61, 62). Subjects were asked about their use of cigarettes, e-cigarettes, and cannabis over their lifetime and in the past year. Subjects also reported on the presence or absence of DSM-5 symptoms of Attention-Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder. The Patient Health Questionnaire-9 (PHQ-9) was included as a measure of depressive symptomatology. Supplemental interview questions, based on the Prototype/Willingness Model of Adolescent Risk Behavior, asked subjects to rate their willingness to smoke one cigarette or one cannabis "joint," and their perceptions of peers who smoke cigarettes and smoke cannabis (59). Of note, questions on adolescents' self-reported cannabis use were inadvertently omitted from the interview at the 11th grade timepoint and thus not available for analysis.

Following the administration of the study interview, phlebotomy was performed to provide DNA from peripheral blood cells and serum for ELISA-based analysis of substance exposure.

Assay Procedures

DNA extraction from whole blood was performed according to our previously published protocols (60), then frozen at −80°C until usage (63).

To determine recent smoke exposure *via* measurement of methylation at cg05575921 (34), 1 μg aliquots of DNA were first bisulfite converted using an Epitect Fast 96 Bisulfite Conversion kit (Qiagen, Germany). Next, converted DNA samples were pre-amped, diluted 1:3000, and then PCR amplified using fluorescent, dual labeled primer probe sets specific for cg05575921 obtained from Behavioral Diagnostics (Coralville, IA, USA) through their distributor IBI Scientific (Dubuque, Iowa, www.ibisci.com) and Universal Digital PCR™ reagents and protocols were obtained from Bio-Rad (Carlsberg, CA, USA). PCR reactions were performed on a Bio-Rad droplet digital PCR (ddPCR), which allows for reference-free measurement of allele proportions (64). In the current study, the alleles of interest were the "C" alleles, corresponding to the methylated cg05575921 cytosine residue, and the "T" allele, corresponding to the unmethylated cg05575921 cytosine residue. The proportion of each allele was analyzed using Bio-Rad's proprietary QuantiSoft™ software and expressed as percent methylated for use in subsequent analyses.

Serum cotinine and cannabinoid values were determined by enzyme linked immunoassay (ELISA) using kits from AbNova (Taiwan) and read on Molecular Devices (Sunnydale, USA) EMax spectrophotometer. All samples were frozen at −80°C until usage (63).

Follow-Up Visits

Repeat venipuncture to obtain whole blood for DNA preparation and serum samples for analysis of substance use were performed again at the 1 year (11th grade) and 2 year (12th grade) timepoints.

Coding Procedures and Data Analysis

All data storage and analyses were conducted on password-protected computers using R version 4.0.0 (65). Epigenetic positivity for smoke exposure was defined as cg05575921 methylation below 80% methylation, a cutoff chosen based on our previously published work for its combination of high sensitivity and specificity (34). Cotinine positivity was defined as a serum value of ≥3 ng/mL, while THC positivity was defined as ≥0.5 ng/mL.

Subjects reported on environmental risk factors for smoking; their answers were subsequently dichotomized as "high" or "low" risk for use in subsequent analyses. Most questions included four possible responses, corresponding to numeric scores of 1–4 and in these cases, 1 and 2 were typically coded as "low" and 3 and 4 as "high" risk. Yes/no questions required no further dichotomization. Responses to whether a subject had a mother, father, or sibling in the home who smoked were dichotomized to "any" or "no" family members in the home who smoked.

Willingness questions asked subjects whether they would be "not at all willing," "kind of willing," or "very willing" to smoke a

cigarette or a "joint" of cannabis. For analysis, these responses were dichotomized into "low" risk ("not at all" or "kind of" willing) vs. "high" risk ("very willing").

Prototype questions asked subjects to rate peers who smoked cigarettes and used cannabis by how "popular," "smart," "cool," "attractive," and "dull or boring" (reversed) they were, with options including "not at all," "a little bit," "kind of," and "very," which corresponded to numeric scores of 1–4. These "Prototype Scores" were then totalled for each substance and the subjects scoring approximately in the top 25th percentile (cutoffs varied depending on the distribution of scores) were coded as being at "high" risk, while the remainder were coded as "low" risk.

The final set of risk factors examined included symptoms of Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and Major Depressive Disorder (MDD) (66). Subjects were coded as having a "high" level of ADHD symptoms if they endorsed ≥6 symptoms in the inattentive and/or hyperactivity/impulsivity categories, a "high" level of ODD symptoms if they endorsed ≥4 symptoms, and a "high" level of CD symptoms if they endorsed ≥3 symptoms. Depressive symptoms were assessed via the PHQ-9 and coded as "high" if they scored ≥10 (67).

Following dichotomization of the above variables, 2x2 tables were constructed for each biomarker x risk factor at each of the three timepoints. Odds Ratios (ORs) were then calculated for each 2x2 table using the *odds ratio.wald()* function in the *epitools* package (68) in R.

Spearman correlations between select variables were calculated using the *cor.test()* function in R. Linear regression models predicting cg05575921 methylation and ANOVA comparisons between groups were calculated using base packages in R.

RESULTS

Subject Characteristics

A total of $n = 448$ subjects enrolled in the study and completed interviews and biomaterial sampling. DNA methylation analyses of cg05575921 were completed for a total of $n = 442$ subjects at the 10th grade timepoint. Of these, 376 (85.1%) returned for the 11th grade assessment and successfully completed DNA methylation analysis, and 366 (82.8%) returned for final assessment in 12th grade and completed DNA methylation analysis. Of these, 437 were successfully assayed for cotinine and 440 for THC at the 10th grade visit; 377 were successfully assayed for serum cotinine and THC at the 11th grade visit, and 364 successfully assayed for serum cotinine and THC at the 12th grade visit.

Clinical and demographic characteristics of the subjects are shown in **Table 1**. At study intake in 10th grade, subjects' age was tightly distributed around 16 years, and the majority were female (55%). The majority were white (84%), and non-Hispanic (84%). Subjects with a household income of below $50,000 per year were defined as "low" income constituting 33% of the sample.

Students' responses to interview questions are also provided in **Table 1**. As shown in the table, 10% of 10th graders reported their parents "rarely" or "never" knew where they were when not at home, and 27% reported their parents knew "only a few" or "none" of their friends. Having a family member who smoked was reported by 27% of subjects. Subjects reported higher rates of cannabis smoking compared to cigarette smoking among their best friends ("most or all." 8 vs. 3%), boyfriend/girlfriend (25 vs. 15%) and other students at their school ("most or all," 35 vs. 21%). Similarly, subjects reported greater willingness ("kind of willing" or "very willing" vs. "not at all willing") to smoke a cannabis joint (17%) than a cigarette (6%).

Subjects were more likely to report favorable perceptions of cannabis smokers than cigarette smokers, with the mean Prototype Score for cannabis users equal to 11.4 (SD 3.7) vs. 9.7 (SD 2.8) for smokers. The difference was highly significant (Wilcoxon signed-rank test W = 70,787, $p = 1.139e\text{-}12$). Due to the different distributions of each Prototype Score, slightly different cutoffs were used to dichotomize subjects into "high" and "low" risk groups, with the cutoff for cannabis equal to 14 (79%ile) and cigarettes equal to 12 (73%ile).

Biomarker and Self-Report Relations

At the 10th grade timepoint, 393 of 437 (90.0%) subjects were negative for all three biomarkers, a figure which declined to 323 (85.7%) in 11th grade and 277 (75.9%) by 12th grade. At each timepoint there were subjects positive for one, two, or all three of the biomarkers, with no perfectly overlapping groups. Each timepoint included subjects positive for cg05575921 (methylation < 80%) that would not have been identified by the serum biomarkers. A total of 24 (5.4%), 21 (6%), and 25 (7%) demonstrated epigenetic positivity for smoke exposure at the 10, 11, and 12th grade timepoints, respectively.

Self-report relationships revealed interesting patterns. In 10th grade, all e-cigarette users were also cigarette users, whereas in 11 and 12th grade the two groups had significantly less overlap. In terms of self-reported cannabis use, roughly one third of users at both the 10th grade and 12th grade timepoints reported also using either cigarettes or e-cigarettes. Relationships between positive self-report of the use of cigarettes, e-cigarettes, and cannabis at each timepoint are available in the form of Venn diagrams as **Supplementary Figure 1**, which also depicts relationships between positivity for each biomarker at all three timepoints. **Supplementary Table 1** additionally provides the number of subjects positive for cotinine, THC, or either one across the three timepoints in each possible combination (e.g., how many subjects were positive for cotinine in 12th grade but not 10th or 11th).

A correlation table depicting relationships between self-report measures and biomarkers across all three timepoints is provided as **Figure 1**. As shown, there were significant relationships between self-reported cigarette use and cotinine cross-sectionally and across timepoints. Relationships between cotinine and self-reported e-cigarette were weaker but still significant cross-sectionally. Interestingly, cotinine positivity was also significantly related to self-reported cannabis use, particularly at the 12th grade timepoint. Epigenetic positivity was significantly related to self-reported cigarette use cross-sectionally and robustly related to cotinine positivity across timepoints, and to a lesser

TABLE 1 | Sample demographics and environmental, and behavioral risk factors for smoking in the 10th grade ($n = 442$), and odds ratios for epigenetic positivity for smoke exposure in 10–12th grade.

Demographic characteristics and risk factors (10th grade)	*N* or Mean (*SD* or Percent)
Age at intake (years)	15.7 (0.6)
Sex (M)	197 (45)
Race (Non-white) ($n = 440$)	70 (16)
Ethnicity (Hispanic)	69 (16)
Household income (<$50k/year)	145 (33)
Probe: "My parents know where I am and who I am with when I am not at home." Answer: "sometimes or rarely" (vs. "always or usually") ($n = 440$)	43 (10)
Probe: "How many of your friends to your parents know?" Answer: "none" or "a few" (vs. "most" or "all") ($n = 440$)	119 (27)
Probe: "How many of your best friends smoke cigarettes?" Answer: "most" or "all" (vs. "none" or "a few") ($n = 439$)	12 (3)
Probe: "How many of your best friends smoke marijuana?" Answer: "most" or "all" (vs. "none" or "a few") ($n = 439$)	37 (8)
Probe: "How many kids at school smoke cigarettes?" Answer: "most" or "all" (vs. "none" or "a few") ($n = 438$)	90 (21)
Probe: "How many kids at school use marijuana" Answer: "most" or "all" (vs. "none" or "a few") ($n = 439$)	154 (35)
†Probe: "Do you have a girlfriend/boyfriend who smokes cigarettes?" Answer: "yes" (vs. "no") ($n = 248$)	36 (15)
†Probe: "Do you have a girlfriend/boyfriend who uses marijuana?" Answer: "yes" (vs. "no") ($n = 244$)	62 (25)
Probe: "Do you have a family member who smokes" Answer: "yes" (vs. "no") ($n = 442$)	120 (27)
Probe: "Would you be willing to smoke a single cigarette?" Answer: "very" or "kind of" willing (vs. "not at all") ($n = 438$)	27 (6)
Probe: "Would you be willing to smoke a single joint?" Answer: "very" or "kind of" willing (vs. "not at all") ($n = 438$)	73 (17)
Smoker Prototype Scale score > 11 (73rd percentile) ($n = 438$)	120 (27)
Cannabis User Prototype Scale score> 14 (79th percentile) ($n = 444$)	94 (21)
ADHD Symptoms – "high" (≥6 symptoms of inattention and/or hyperactivity/impulsivity) ($n = 442$)	104 (24)
ODD Symptoms –"high" (≥4 symptoms) ($n = 434$)	62 (14)
CD Symptoms – "high" (≥3 or more symptoms) ($n = 442$)	69 (16)
MDD Symptoms – "high" (PHQ-9 score ≥ 9)	59 (13)

ADHD, Attention-Deficit/Hyperactivity Disorder; ODD, Oppositional-Defiant Disorder; CD, Conduct Disorder.
†Only participants who endorsed having a boyfriend/girlfriend were asked this question.

degree, THC positivity. Interestingly, it was unrelated to self-reported past year e-cigarette use and cannabis use at any timepoint. Finally, and unsurprisingly, biomarker positivity at one timepoint was generally associated with positivity for the same biomarker at other timepoints.

To address the issue of subject dropout between 10 and 12th grade influencing the above analyses, we tested whether subjects who completed their 10th grade but not 12th grade visit had differing rates of biomarker positivity. Chi-square analysis of each biomarker vs. dropout by 12th grade revealed no significant relationships (all $p > 0.05$).

Given the modest associations between positivity serum biomarkers (cotinine and THC) and cg05575921 methylation at the chosen cutoffs, these relationships were examined in a linear fashion using simple regression models. As shown in **Supplementary Figure 2**, linear relationships between cg05575921 methylation and serum cotinine (a) and serum THC (b) were stronger than for the binary relationships (all $p < 0.001$). Linear relationships between cg05575921 methylation and cotinine were stronger ($R = -0.4$ to -0.55) than those between cg05575921 methylation and THC (-0.21 to -0.37) at each timepoint, and consistent with our prior findings (69).

Effect of Tobacco and Cannabis Co-use on Methylation Levels

Next, we examined whether adolescents with serum evidence of tobacco and cannabis co-use had greater epigenetic changes. **Figure 2** depicts boxplots of DNA methylation at cg05575921 for the 12th grade timepoint stratified by cotinine positivity vs. negativity and THC positivity vs. negativity. Those positive for either THC (85.9%) or cotinine (mean 84.4%) had lower average methylation than those negative for both (mean 86.8%),

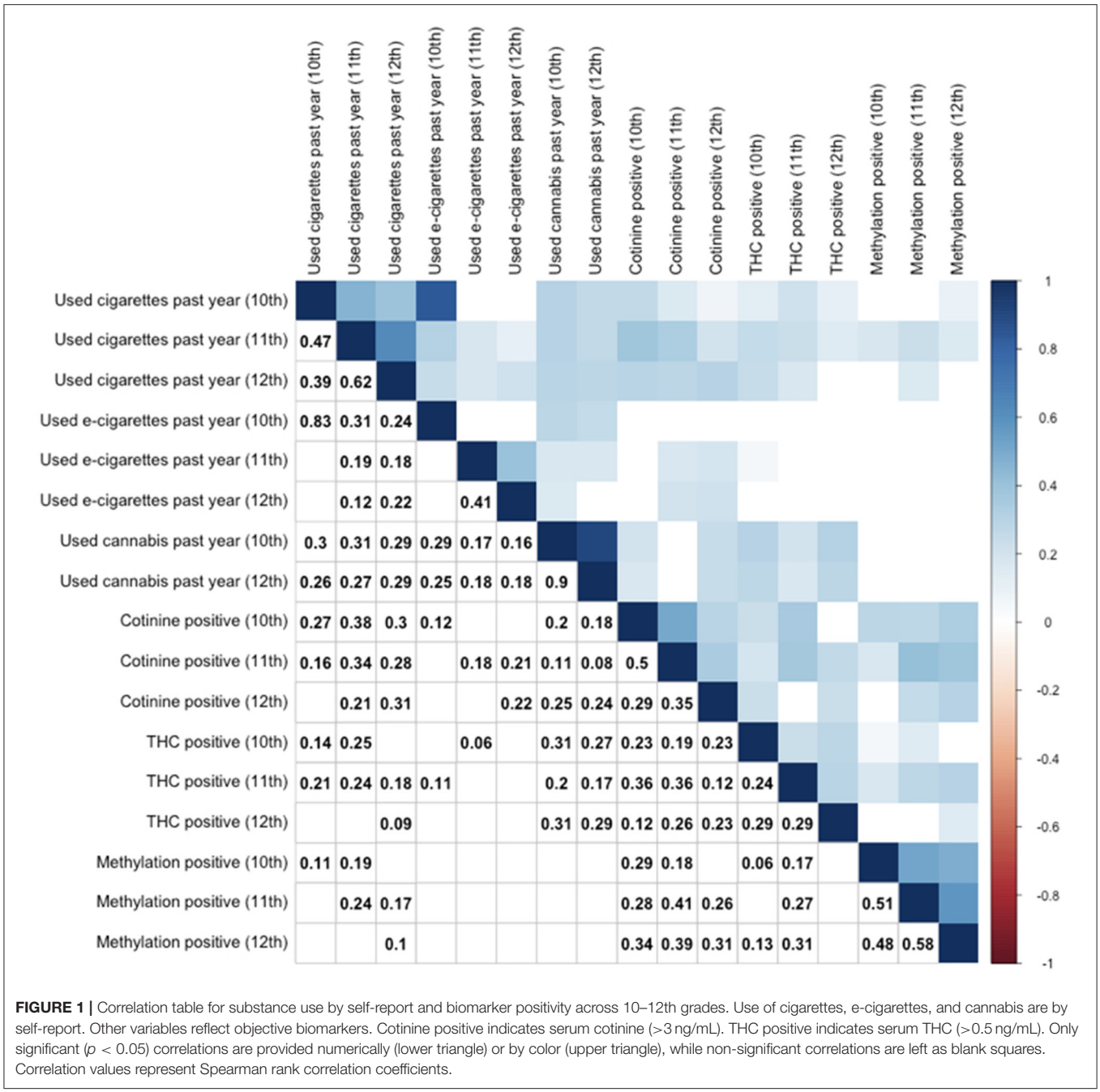

FIGURE 1 | Correlation table for substance use by self-report and biomarker positivity across 10–12th grades. Use of cigarettes, e-cigarettes, and cannabis are by self-report. Other variables reflect objective biomarkers. Cotinine positive indicates serum cotinine (>3 ng/mL). THC positive indicates serum THC (>0.5 ng/mL). Only significant ($p < 0.05$) correlations are provided numerically (lower triangle) or by color (upper triangle), while non-significant correlations are left as blank squares. Correlation values represent Spearman rank correlation coefficients.

and the difference was significant between those positive for cotinine only and those negative for both ($p < 0.05$). Those positive for both THC and cotinine had the lowest average methylation (mean 77.5%), and their average methylation was significantly different from each of the other groups (all $p < 0.05$), and most significantly different from those negative for both ($p < 0.001$).

To address the possibility that lower methylation cg05575921 methylation levels in tobacco and cannabis dual users was simply due to greater tobacco smoke exposure, we examined whether linear regression models predicting methylation levels would show a significant effect of serum THC after adjustment for serum cotinine. At the 10th grade timepoint, THC was not a significant predictor of methylation ($p = 0.29$) with the inclusion of cotinine as an additional predictor. However, at both the 11th grade and 12th grade timepoints, THC was a highly significant predictor (both $p < 0.001$). Further, the addition of THC to cotinine as a linear predictor of cg05575921 methylation significantly improved model fit at both the 11th grade [$F_{(1,378)} = 46.58$, $p < 0.001$] and 12th grade [$F_{(1,366)} = 29.42$, $p < 0.001$] timepoints compared to cotinine alone.

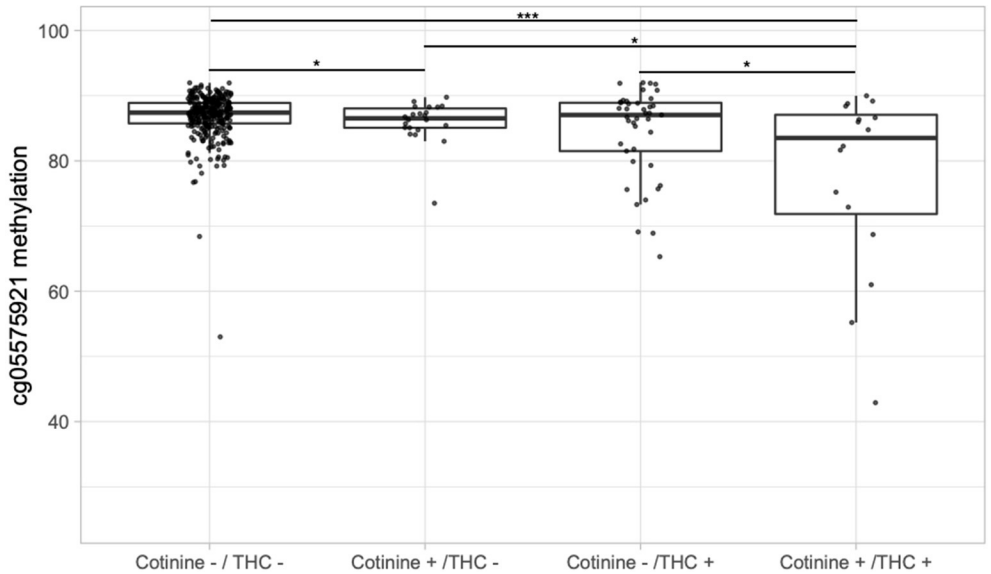

FIGURE 2 | Boxplots of DNA methylation at cg05575921 vs. serum cotinine and/or THC positivity in the 12th grade. "Cotinine +" indicates > 3 ng/mL and "THC +" indicates > 0.5 ng/mL. Significance codes: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ (Tukey's Honest Significant Difference).

Risk Factors Predicting Biomarker Positivity

Subjects provided information on a variety of risk factors known to be associated with adolescent smoking, including their family environment, peer and school environment, personal willingness, and smoker Prototypes (tobacco and cannabis) (58, 59, 70), and internalizing and externalizing psychopathology. These risk factors were then used as predictors of positivity for epigenetic positivity and serum cotinine and THC positivity at the 10, 11, and 12th grade timepoints.

Figure 3 depicts the calculated Odds Ratio (OR) of positivity for our epigenetic biomarker and our serum biomarkers, cotinine and THC, across the three timepoints, also available as **Supplementary Tables 2–4**. Note that for the 10th grade timepoint, these ORs represent cross-sectional rather than prospective associations. Broadly speaking, the number of risk factors for epigenetic positivity increased from 10th grade to 12th grade, while the opposite was true for cotinine and THC positivity. For example, in the 10th grade, low income was associated with a significantly increased OR (2.54) of epigenetic positivity, while sex and race were not associated. Other risk factors significantly associated with epigenetic positivity in 10th grade included low parental supervision, a significant other using cannabis, and willingness to smoke a cigarette. By 12th grade, best friends using cannabis, use of cannabis by peers, willingness to smoke a joint, and subjects' perception of cannabis users (Prototype Score) all became significant predictors, as did family member cigarette smoking.

For cotinine, nearly every risk factor was significantly associated with positivity at the 10th grade timepoint. By 12th grade, the strongest risk factors for cotinine positivity included low parental supervision, how many friends used cannabis, and willingness to smoke one joint. For THC positivity, the most associated risk factor in 10th grade was willingness to smoke one joint. By 12th grade, the number of friends using cannabis became the most significant risk factor.

Across timepoints and biomarkers, parental supervision was the risk factor most consistently associated with positivity, being a significant predictor in each analysis. Having a significant other who used cannabis, willingness to smoke one joint, and high levels of CD symptoms were significant predictors in each analysis but one.

DISCUSSION

In this study we examined relationships between various risk factors for tobacco and cannabis smoking and an emerging epigenetic biomarker for smoke exposure, DNA methylation of the genomic CpG cg05575921. Our Eastern Iowa adolescents' responses reflect broader changes seen over the past two decades in that many more reported having friends and significant others who used cannabis compared to smoking cigarettes. Similarly, adolescents perceived cannabis users more positively than cigarette smokers, and were more willing to smoke a joint than a cigarette. Interestingly, these patterns were not reflected in indicators of nicotine (serum cotinine) vs. smoke exposure (cg05575921 methylation) across the 10th grade through 12th grades. The finding that more subjects were positive for serum cotinine than serum THC at each timepoint could be due to e-cigarette use. Examination of our epigenetic biomarker for smoke exposure showed significant overlap with serum biomarkers but also revealed some subjects at each timepoint for whom the smoke exposure would not have been otherwise detected.

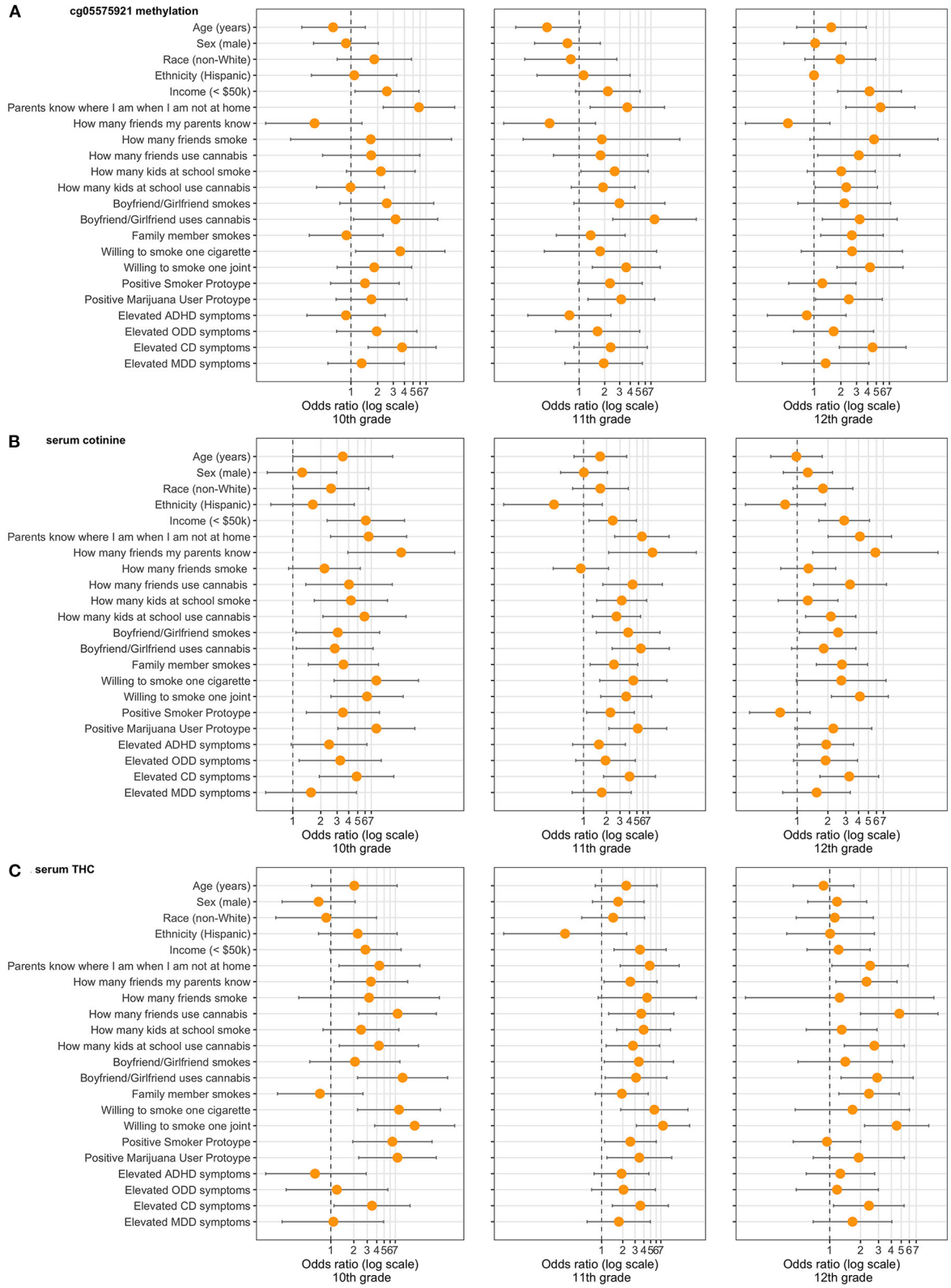

FIGURE 3 | Demographic, environmental, and behavioral risk factors ascertained in 10th grade and Odds Ratios for **(A)** epigenetic positivity (cg05575921 methylation), **(B)** cotinine positivity (>3 ng/mL), and **(C)** THC positivity (>0.5 ng/mL) positivity in 10–12th grade ($n = 442$). Only participants who endorsed having a

(Continued)

FIGURE 3 | boyfriend/girlfriend were asked questions regarding the significant other using cigarettes or cannabis. "Parents know where I am when not at home" refers to "sometimes or rarely." "How many friends my parents know" refers to "none or a few." "How many friends smoke" and "How many friends use cannabis" refer to "most or all." "How many kids at school smoke" and "How many kids at school use cannabis" refers to "most or all." "Willing to smoke one cigarette" and "Willing to smoke one joint" refer to "very or kind of." "Positive Smoker Prototype" refers to 73rd percentile and above. "Positive Marijuana User Prototype" refers to 79th percentile and above. "Elevated ADHD symptoms" refers to 6 or more inattentive and/or hyperactive/impulsive. "Elevated ODD symptoms" refers to 4 or more. "Elevated CD symptoms" refers to 3 or more. "Elevated MDD symptoms" refers to 9 or more on the PHQ-9. All Odds Ratios computed by unconditional maximum likelihood (Wald) tests.

Relationships between risk factors and positivity for our biomarkers showed substantial overlap at each timepoint, consistent with expectations that many risk factors for substance use are non-specific. We also observed an increasing proportion of high schoolers demonstrating epigenetic positivity for smoke exposure, defined as cg05575921 methylation <80%, as they progressed from 10 to 12th grade, consistent with decades of research indicating that late adolescence is a period of peak risk for the initiation of smoking. By 12th grade, this resulted in a doubling of risk factors being significantly associated with epigenetic positivity for smoke exposure, whereas an opposite trend was seen for serum cotinine and THC positivity, with fewer risk factors remaining significantly associated in 12th grade as compared to 10 and 11th grade. These contrasting patterns may reflect the fact that we chose fairly low cutoffs for positivity for our serum biomarkers in order to maximize sensitivity. Over time we would thus expect to see decreased ORs for some risk factors as more adolescents in various "low risk" groups begin using. In contrast, because epigenetic positivity requires cumulative exposure to smoke for methylation at cg05575921 to decrease from a population average of around 86% to below 80%, our finding that more risk factors became significant over time is expected.

In terms of specific risk factors analyzed, it is not surprising that lower parental supervision was robustly associated with an increased odds of biomarker positivity. Best friends' and significant others' use of cannabis were significant risk factor for positivity for multiple biomarkers at multiple timepoints. Whereas, low income was strongly associated with increased risk, race and ethnicity were not associated with a greater or lower risk, though this negative finding may reflect the relatively low number of non-white and Hispanic subjects in our sample. Similarly, because only 3% of subjects reported they had best friends who smoked cigarettes in 10th grade, our study may not have been adequately powered to examine this risk factor. As expected, both willingness to smoke cigarettes and cannabis as well as prototypes of smokers of each substance were associated with positivity at one or more timepoints for each biomarker (59). Lastly, CD symptoms were significantly associated with positivity for each biomarker at each timepoint with the exception of epigenetic positivity in 11th grade. In contrast, although ADHD and ODD symptoms are known risk factors for smoking, these associations were generally not significant in our sample, nor were depressive symptoms.

Our results also provide evidence that co-users of tobacco and cannabis on average have greater cumulative exposure to smoke and its toxic components (44), including PAHs (71). By 12th grade, those positive for both cotinine and THC showed a significantly lower average methylation at cg05575921 than those positive for THC alone ($p < 0.001$), cotinine alone ($p < 0.001$), or negative for both ($p < 0.001$). This is consistent with two recent studies reporting highly significant demethylation of cg05575921 in cannabis and tobacco co-users (72, 73). Interestingly, Osborne and colleagues (73) reported no CpGs significantly associated with exclusive cannabis use, suggesting that tobacco use may dominate or mask signatures specific to cannabis and/or THC. To address this possibility, the recent study of Markunas et al. (74) controlled for tobacco exposure in their epigenome-wide association study of lifetime cannabis use, finding modest evidence of association with the CpG cg15973234 in the gene *CEMIP*.

An alternative interpretation of our findings is that co-users of tobacco and cannabis may simply be exposed to more tobacco smoke than tobacco smokers who do not use cannabis. Although limitations in our self-report data do not allow us to examine this possibility directly, linear regression models controlling for serum cotinine did show a significant independent effect of serum THC on cg05575921 methylation at the 11 and 12th grade timepoints, suggesting greater tobacco smoke exposure is not solely responsible for lower methylation in the dual-use group. In addition, *post-hoc* analysis of serum cotinine and THC values in the 12th grade suggest greater change in cg05575921 methylation in dual users may be due to heavier cannabis use. Mean serum cotinine was slightly higher in the cotinine positive, THC negative group (53.1 ng/mL) than in the group positive for both substances (41.9 ng/mL), whereas mean serum THC levels were higher in the dual use group (4.9 ng/mL) than in the group only positive for THC (2.7 ng/mL). However, the latter difference was only significant at the trend level ($p < 0.10$).

E-cigarette use in our study was not significantly correlated with demethylation of cg05575921, despite the fact that e-cigarette use predisposes to future combusted tobacco use (20). This is likely because e-cigarettes are not thought to expose users to sufficient levels of PAHs (75) to induce demethylation of cg05575921. E-cigarette use may also explain the weaker correlations between cotinine positivity and epigenetic positivity compared to self-reported cigarette smoking and epigenetic positivity, as the cotinine positive group likely contains both cigarette users and e-cigarette users.

In considering the results above, several limitations or alternate explanations are worth mentioning. First, secondhand smoke exposure may explain the association between some risk factors and epigenetic positivity, particularly the presence of smokers in the home, although this effect is likely modest (76). A second limitation, subject dropout, is a potential concern as this could bias observed relationships between risk factors

and biomarker positivity. It would be expected that dropouts would be those more likely to be engaging in risk behaviors in general. However, analysis of subjects who completed the 10th grade but not 12th grade visits did not reveal significant differences between groups for any biomarker in 10th grade. Third, although we selected adolescents at higher risk than the general population due to having a friend or family member who smokes cigarettes, our sample had a limited proportion of socioeconomically disadvantaged and ethnic/racial minority subjects, limiting generalizability to these groups. Our small sample size may also have limited our ability to detect significant associations between some risk factors and biomarker positivity, particularly at the 12th grade timepoint.

The most significant limitation of the epigenetic technology discussed above may be its insensitivity to pure e-cigarette use. The large proportion of subjects were e-cigarette users in 12th grade (54/364) may also explain our finding that the correlations between cg05575921 methylation and cotinine positivity at each timepoint, though significant, were modest (0.29 – 0.41), with linear relationships being somewhat stronger. This suggests the need to develop more specific biomarkers for non-combusted nicotine use, and that cg05575921 may be best thought of as an additional screening tool rather than replacement for conventional biomarkers and other methods of detecting substance use in adolescents. The high rate of e-cigarette use also suggests that public health campaigns designed to shift adolescents' perception of "typical" e-cigarette users (Prototypes) toward the negative may be helpful, similar to past effects observed with cigarette smokers (77).

Ethical concerns in the use of an epigenetic biomarker to study smoking in adolescent populations are an important consideration. While these concerns should be balanced against the public health impact of smoking, the largest preventable cause of mortality in the US, it is important to note that laboratory testing, whether conventional or epigenetic, is generally not supported as a standalone screening or assessment for substance use (78), and that children and adolescents are inherently more vulnerable than adults, placing greater burden on the clinician in weighing the costs and benefits of such testing.

In summary, the epigenetic biomarker cg05575921 can provide a window into changing patterns of nicotine, tobacco, and cannabis use in adolescence. Our analyses suggest that in addition to being a highly sensitive biomarker for tobacco smoke, cg05575921 methylation may also be a novel tool for detecting cannabis smoking in adolescents, and further study of its utility in larger samples of pure cannabis users is warranted. Going forward, cg05575921 may have a role in as a clinical screening tool, complementing self-report and other methods of assessing substance use in adolescents. At the same time, because the biomarker is insensitive to pure e-cigarette use, other screening methods, including high quality interview-based measures (79), will continue to be essential clinical tools.

PRESENTATION INFORMATION

This study was presented as an abstract at the American Academy of Child and Adolescent Psychiatry's 67th Virtual Annual Meeting, October 12–24th, 2020.

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 Iowa's Institutional Review Board (IRB ID # 201409705). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RP and MG obtained funding for this study and developed key concepts. AA performed the initial analyses and wrote the manuscript. RP, MG, and FG edited the manuscript extensively. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.688384/full#supplementary-material

Supplemental Figure 1 | Venn diagrams of **(A)** positivity for serum cotinine (>3 ng/mL), serum THC (>0.5 ng/mL), and cg05575921 methylation (<80%) and **(B)** self-reported use of cannabis, cigarettes, and e-cigarettes in the past year, 10–12th grades. Self-reported cannabis use was not available for analysis at the 11th grade timepoint.

Supplemental Figure 2 | Linear fits of cg05575921 methylation vs. serum cotinine and THC at the **(A)** 10th, **(B)** 11th, and **(C)** 12th grade timepoints.

Supplementary Table 1 | Positivity for cotinine, THC, or either at 10, 11, and 12th grades.

Supplementary Table 2 | Environmental, and behavioral risk factors for smoking in the 10th grade ($n = 442$), and odds ratios for epigenetic positivity for smoke exposure in 10–12th grade.

Supplementary Table 3 | Demographic, environmental, and behavioral risk factors ascertained in 10th grade and odds ratios for cotinine positivity in 10–12th grade ($n = 442$).

Supplementary Table 4 | Demographic, environmental, and behavioral risk factors ascertained in 10th grade and odds ratios for THC positivity in 10–12th grade ($n = 442$).

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Effect of Transcutaneous Auricular Vagus Nerve Stimulation on Protracted Alcohol Withdrawal Symptoms in Male Alcohol-Dependent Patients

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Protracted alcohol withdrawal symptoms (PAWS), characterized by the presence of substance-specific signs and symptoms (including anxiety, irritability, mood instability, insomnia, and cravings), make alcohol abstinence difficult and increase the risk of relapse in recovering alcoholics. The goal of this study was to evaluate the effect of transcutaneous auricular vagus nerve stimulation (taVNS) on PAWS and plasma brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and leptin levels in patients with alcohol dependency. A total of 114 patients with alcohol dependence were randomly divided into two groups: the treatment group and the control group. The patients in the treatment group were treated with taVNS of the bilateral auricular concha using an ear vagus nerve stimulator. The Pennsylvania Alcohol Craving Scale was used to evaluate the extent of craving for alcohol. The Self-Rating Anxiety Scale and Self-Rating Depression Scale (SDS) were used to evaluate the extent of anxiety and depression symptoms, respectively. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality. Enzyme-linked immunosorbent assay was used to measure plasma BDNF, IL-6, TNF-α, and leptin levels. The results showed that the SDS and PSQI scores were significantly lower in the treatment group than in the control group. Moreover, compared with the control group, the average BDNF levels in the treatment group were significantly increased. These results suggest that taVNS could improve the depression symptoms and sleep quality in alcohol-dependent patients after withdrawal, which might be related to the upregulation of plasma BDNF levels.

Keywords: alcohol dependence, brain-derived neurotrophic factor, depression, protracted alcohol withdrawal symptoms, sleep quality, transcutaneous auricular vagus nerve stimulation

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INTRODUCTION

It has been estimated that 3 million people die every year due to the harmful use of alcohol according to the data of the World Health Organization, which causes great health and economic losses to individuals and society. A high relapse rate is a difficult problem in the treatment of patients with alcohol dependence. It has been reported that ∼90% of alcoholics may experience at least one relapse within 4 years after treatment (1), which may be related to protracted alcohol withdrawal symptoms (PAWS) (2).

PAWS, a cluster of symptoms that occurs because of the sudden cessation of alcohol consumption after chronic or prolonged ingestion, includes anxiety, irritability, mood instability, insomnia, and craving (3). These withdrawal symptoms make attempts to abstain from alcohol difficult and increase the risk of relapse in recovering alcoholics. Therefore, it is of great significance to prevent relapse by reducing withdrawal symptoms in patients with alcohol dependence. At present, drug therapy is mainly used to treat PAWS in patients with alcohol dependency. Given that the liver and kidney functions of alcohol-dependent patients are impaired, the use of drugs may further increase the burden of the liver and kidney. Thus, there is an urgent need to find a safe method to treat PAWS.

Non-invasive transcutaneous auricular vagus nerve stimulation (taVNS) stimulates the auricular branch of the vagus nerve through the outer ear in humans by placing an electrode on the corresponding auriculate acupoint (4). This method avoids trauma pain and fear of acupuncture, making it more easily accepted by patients (5). There is evidence that intermittent and chronic stimulation of taVNS is widely used to treat drug-resistant epilepsy (6), depression (7, 8), and insomnia (9). Because of its good safety and potential therapeutic effects on withdrawal symptoms, taVNS may be a useful, non-pharmacological, and non-invasive approach that yields beneficial effects for PAWS management in individuals with alcohol dependence.

Brain-derived neurotrophic factor (BDNF) is associated with many neuropsychiatric diseases, including alcohol use disorders and depression. It has been shown that the level of BDNF in patients with alcoholism was significantly lower than that in healthy volunteers (10). A further study indicated that the level of BDNF in the serum of alcohol-dependent patients after abstinence was significantly lower than that before abstinence (11). Moreover, low serum BDNF has been found to be associated with suicidal ideation in major depressive disorder (12). A large number of studies have shown that vagus nerve stimulation (VNS) improves the symptoms of several diseases including ischemic stroke (13), Parkinson's disease (14), and depression (15), possibly in conjunction with the upregulated expression of BDNF. Thus, the effect of taVNS on plasma BDNF levels and the relationship between PAWS and plasma BDNF levels were investigated in the present study.

Elevated peripheral immune factors have been demonstrated to be associated with altered mood and memory in patients with current or recent alcohol dependence (16). Moreover, the levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in peripheral blood have been observed to be positively correlated with craving during alcohol withdrawal (17). Considering that recent data have suggested the anti-inflammatory role of VNS (18), whether these inflammatory cytokines could be affected by taVNS in alcohol-dependent patients was also evaluated in the present study.

Leptin, the first discovered and the most studied adipokine, maintains energy homeostasis and controls body weight (19). Accumulating evidence has shown that leptin may modulate withdrawal-induced craving in alcoholic individuals (20, 21). Serum leptin levels have been reported to be altered in alcohol-dependent patients (22, 23). Moreover, a close relationship between serum leptin levels and alcohol craving in both sexes has been observed (24). However, no studies have been conducted on the relationship between leptin and PAWS in patients with alcohol dependency. In addition, the serum levels of leptin have been observed to be decreased in animals that received VNS compared to control animals (25). Thus, the effect of taVNS on plasma leptin levels in patients with alcohol dependency was investigated.

Based on these findings, we hypothesized that taVNS could ameliorate PAWS in alcohol-dependent patients, the mechanism of which may be related to its regulation of plasma BDNF, IL-6, TNF-α, and leptin levels. To test this hypothesis, a total of 114 patients with alcohol dependence were randomly divided into two groups: the treatment and control groups. The patients in the treatment group were treated with taVNS of the bilateral auricular concha using an ear vagus nerve stimulator. The Pennsylvania Alcohol Craving Scale (PACS), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Pittsburgh Sleep Quality Index (PSQI) were used to evaluate the extent of PAWS. Enzyme-linked immunosorbent assay (ELISA) was used to measure plasma BDNF, IL-6, TNF-α, and leptin levels.

MATERIALS AND METHODS

Patients

This study was conducted at the Hefei Fourth People's Hospital, Anhui Mental Health Center, between September 2019 and December 2020. A total of 114 patients with alcohol dependence were enrolled by an experienced and trained researcher (Yi Zhai) in accordance with the guidelines of the structured clinical interview according to the "International Classification of Diseases 10th Revision" criteria. All the patients were male inpatients. All of them were in the drinking period when they were sent to the hospital. They underwent the benzodiazepine substitution for decreasing dependence therapy (for ∼1 week) and were in a stable period of alcohol withdrawal at the time of enrollment. The criteria for joining the group were as follows: (1) age 18 to 65 years, (2) currently not receiving any medication, and (3) gave written informed consent to participate in the study. The exclusion criteria were as follows: (1) serious heart, liver, or kidney diseases, and (2) experiencing other mental illnesses. In accordance with the principles of the Declaration of Helsinki, all patients provided informed written consent prior to participation. This study was approved by the Ethics Committee of the Hefei Fourth People's Hospital, Anhui Mental Health Center.

Study Design

A total of 114 patients with alcohol dependence were randomly divided into two groups: the treatment group ($n = 58$) and control group ($n = 56$). The patients in the treatment group were treated with taVNS of the bilateral auricular concha using an ear vagus nerve stimulator. The patients in the control group wore the same instrument without power. All the patients underwent the benzodiazepine substitution for decreasing dependence therapy (for ∼1 week) and were in a stable period of alcohol withdrawal at the time of enrollment before taVNS treatment or negative stimulation. The taVNS device was operated according to a previously described method (26). Briefly, the stimulation frequency of the taVNS was 20 Hz, and the intensity was increased gradually from 0.4 to 1.0 mA according to the tolerance of the patient. Transcutaneous stimulation was performed three times a day, 30 min per session. The treatment period was 4 weeks. The blood samples and scale scores of all the patients were collected before and after the treatment.

Clinical Data and Scale Score Measurements

The PACS was used to evaluate the extent of the craving for alcohol. The SAS and SDS were used to evaluate the extent of anxiety and depression symptoms, respectively. The PSQI was used to assess sleep quality. A demographic questionnaire was used to collect general information about the participants. According to the conclusion of the other studies (27, 28), the boundary values of the SAS scale anxiety state and the SDS scale depression state were both 50 points. In terms of PSQI, scores > 5 indicate poor sleep quality (29).

Biochemical Measurements

Blood samples were taken from the vein of the participant between 8:00 a.m. and 9:00 a.m. at the end of an overnight fasting period of 10–11 h at baseline before taVNS treatment and on the next morning after last taVNS treatment. Tubes containing ethylenediaminetetraacetic acid were used to collect the samples. The blood samples were immediately centrifuged at 3,000 rpm for 5 min at 4°C. The supernatant was extracted as the plasma sample. The extracted plasma was stored at −80°C until detection. Commercially available ELISA kits were used to measure the plasma concentrations of leptin, BDNF, IL-6, and TNF-α (Jianglai Bio, Shanghai, China) according to the instructions of the manufacturer. The assay sensitivities for leptin, IL-6, TNF-α, and BDNF were 0.1, 10, 1.0, and 1.0 pg/ml, respectively, with an intra-assay variation of <9.0% and an inter-assay variation of <11.0%.

Sample Size

The sample size was calculated according to the changes in the depression scores based on the study conducted by Tseng et al. (30). It was calculated considering a 95% confidence interval, 80% power ($\alpha = 0.05$, $\beta = 0.2$), and the related mean and standard deviation (SD) of the depression scores in the aforementioned study ($\mu 1 = 5.35$; $\mu 2 = 8.58$; $SD1 = 2.08$; $SD2 = 3.53$). The minimum sample size was 51 for each group. A total of 114 patients were recruited for the present study.

TABLE 1 | Comparison of baseline data of mean values (or ratios) of demographic data, alcohol-related data, scale scores, and plasma BDNF, IL-6, TNF-α, and leptin levels in the treatment and control groups (mean ± SEM).

Variables	Control group	Treatment group	Statistics (t/χ^2)	*P*
Age	41.38 ± 0.87	40.00 ± 0.89	1.094	0.277
BMI (kg/m²)	21.55 ± 0.41	22.02 ± 0.36	0.867	0.387
Educational status (years)	10.02 ± 0.48	10.47 ± 0.49	0.658	0.512
Years of drinking	17.35 ± 0.94	15.78 ± 0.98	1.157	0.250
Daily intake (standard drink)	7.00 ± 1.26	6.41 ± 0.47	0.546	0.588
PACS score	7.25 ± 0.59	7.96 ± 0.83	0.701	0.485
SDS score	46.87 ± 1.36	49.03 ± 1.62	0.111	0.307
SAS score	43.33 ± 1.15	45.43 ± 1.33	1.198	0.233
PSQI score	6.86 ± 0.54	7.67 ± 0.59	0.348	0.316
leptin (ng/ml)	8.47 ± 0.24	8.12 ± 0.21	1.114	0.267
IL-6 (pg/ml)	30.22 ± 0.70	29.71 ± 0.55	0.588	0.558
TNF-α (pg/ml)	49.72 ± 1.23	49.03 ± 1.14	0.408	0.684
BDNF (ng/ml)	41.95 ± 0.74	40.36 ± 0.72	1.517	0.132

BMI, body mass index; SEM, standard error of mean.

Statistical Analysis

The data were analyzed using SPSS (version 17.0; IBM Corp., Armonk, NY, USA). The differences in the baseline measurements between the two groups were analyzed using a *t*-test. After a 4-week treatment, an analysis of covariance (ANCOVA) was performed to compare the plasma concentrations of leptin, BDNF, IL-6, and TNF-α and the scores of the scales between the two groups, controlling for the respective baseline measurements by using these variables as covariates. The statistical significance was set at $p < 0.05$.

RESULTS

Baseline Data of Demographic Values; Alcohol-Related Data; Plasma BDNF, IL-6, TNF-α, and Leptin Levels; and Scales of the Treatment and Control Groups

As shown in **Table 1**, there were no significant differences in the age, body mass index, educational status, years of drinking, or the daily intake between the two groups.

In terms of scales, compared with the control group, there was no difference in the average scores of the PACS, SDS, SAS, and PSQI in the treatment group (**Table 1**). With 50 points as the critical value (both for SAS and SDS), 18 people were considered to have anxiety symptoms, with a prevalence of 15.8% (18/114), and 20 people were considered to have depression symptoms, with a prevalence of 17.5% (20/114). With 5 points as the critical value for PSQI, 59 people were considered to have sleeping problems, with a prevalence of 51.8% (59/114).

Table 1 shows that the differences between the groups were not statistically significant in terms of plasma leptin, IL-6, TNF-α, and BDNF levels.

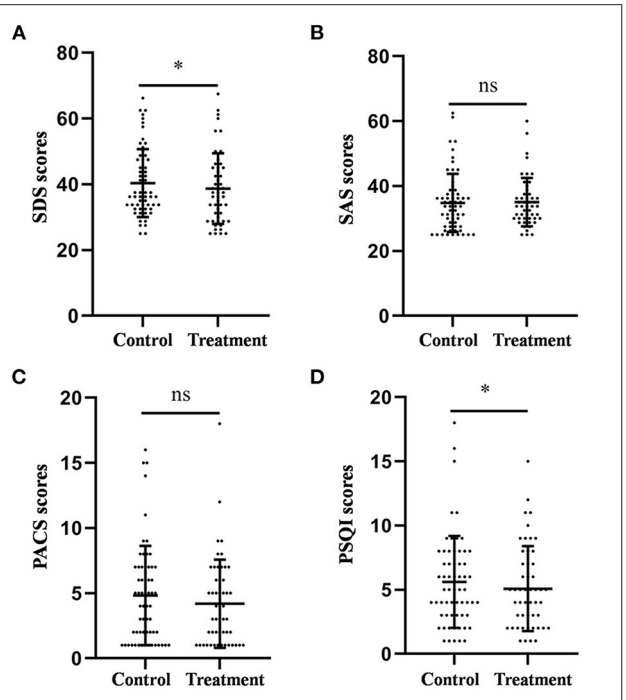

FIGURE 1 | Comparison of the scores of the SDS **(A)**, SAS **(B)**, PACS **(C)**, and PSQI **(D)** between the treatment group and the control group after 4-week treatment. *$P < 0.05$, was considered statistically significant.

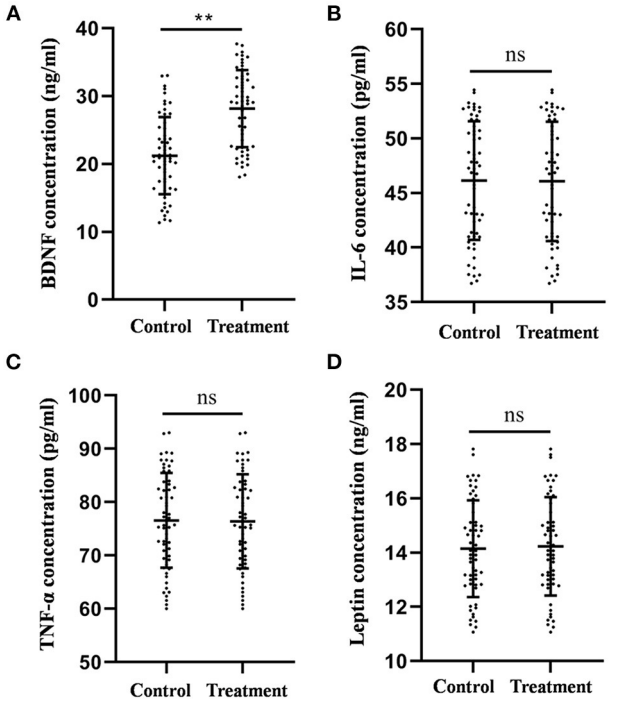

FIGURE 2 | Comparison of the plasma BDNF **(A)**, IL-6 **(B)**, TNF-α **(C)**, and leptin **(D)** levels between the treatment group and the control group after 4-week treatment. **$P < 0.01$, was considered statistically significant.

Effects of Auricular Acupressure on the Scores of Depression-, Anxiety-, Craving-, and Sleep Quality-Related Scales

The average SDS scores of the control and treatment groups were 40.38 ± 1.31 and 37.11 ± 1.29, respectively. As shown in **Figure 1**, the results of the ANCOVA showed that the SDS score in the treatment group was significantly lower than that in the control group ($F = 5.987$, $p = 0.016$, **Figure 1A**).

The average PSQI scores of the control and treatment groups were 5.61 ± 0.46 and 4.88 ± 0.43, respectively. Similarly, the PSQI score in the treatment group was significantly lower than that in the control group ($F = 4.104$, $p = 0.045$, **Figure 1D**).

The average SAS scores of the control and treatment groups were 34.80 ± 1.15 and 35.05 ± 1.05, respectively. The average PACS scores of the control and treatment groups were 4.82 ± 0.49 and 3.92 ± 0.39, respectively. The results of the ANCOVA showed that there was no difference in the scores of anxiety ($F = 0.314$, $p = 0.576$, **Figure 1B**) and craving ($F = 1.567$, $p = 0.214$, **Figure 1C**) between the two groups.

Taken together, these results suggest that auricular acupressure could improve depression and sleep quality; however, it had no significant effect on anxiety and craving in patients with alcohol dependence after withdrawal.

Effects of Auricular Acupressure on the Plasma BDNF, IL-6, TNF-α, and Leptin Levels

The mean BDNF levels in the control and treatment groups were 21.23 ± 0.73 and 28.17 ± 0.76 ng/ml, respectively. As shown in **Figure 2**, the results of the ANCOVA showed that the mean BDNF levels were significantly higher in the treatment group than in the control group ($F = 38.978$, $p < 0.001$, **Figure 2A**).

The mean IL-6 levels in the control and treatment groups were 46.13 ± 0.71 and 46.06 ± 0.73 pg/ml, respectively. The mean TNF-α levels of the control group and the treatment group were 76.58 ± 1.16 and 76.40 ± 1.18 pg/ml, respectively. The mean leptin levels in the control and treatment groups were 14.15 ± 0.23 and 14.23 ± 0.24 ng/ml, respectively. No statistical difference was observed in IL-6 ($F = 0.058$, $p = 0.210$, **Figure 2B**), TNF-α ($F = 0.030$, $p = 0.862$, **Figure 2C**), and leptin ($F = 0.039$, $p = 0.843$, **Figure 2D**) levels between the two groups according to the results of the ANCOVA.

Collectively, these results indicate that auricular acupressure could increase plasma BDNF levels; however, it had no significant effect on the levels of IL-6, TNF-α, and leptin.

DISCUSSION

The present study is the first to demonstrate that taVNS could improve depression and sleep quality in patients with alcohol dependence after withdrawal. Moreover, the results of the ANCOVA showed that the plasma BDNF levels were significantly increased in patients receiving taVNS treatment. These results suggest that taVNS could improve depression symptoms and sleep quality in alcohol-dependent patients after withdrawal, which might be related to the upregulation of plasma BDNF levels.

PAWS, a response to the reduction or termination of alcohol exposure, is considered the core feature of patients with alcohol dependence (31). Negative affective states, such as anxiety and depression, and decline in the cognitive function associated with alcohol withdrawal represent the cause of excessive alcohol consumption and may explain a relapse into alcoholism (32). The PACS, one of the most widely used tools to measure the craving for alcohol, has demonstrated reliability and validity in numerous studies (33, 34). The SAS and SDS are widely used as screening tools, covering affective, psychological, and somatic symptoms associated with anxiety and depression, respectively (21, 35). The PSQI, a 19-item self-report questionnaire that measures subjective sleep quality, has shown good reliability and validity for both healthy and clinical groups with mental and physical health problems (36). Therefore, to evaluate the degree of PAWS in patients with alcohol dependence after withdrawal, the PACS, SAS, SDS, and PSQI were selected to assess the extent of craving for alcohol, anxiety symptoms, depression symptoms, and sleep quality, respectively.

taVNS, as a non-invasive intervention, has beneficial effects on a wide range of neurological, psychiatric, and medical conditions based on clinical observations. Animal experiments and clinical trials have demonstrated that taVNS in the auricular concha region elicits therapeutic effects on depression symptoms (37, 38). Moreover, VNS was approved by the United States Food and Drug Administration in 2005 for treating chronic refractory depression (39). Furthermore, the 2014 "Evidence-based Guidelines of Clinical Practice with Acupuncture and Moxibustion: Depression" also recommended electroacupuncture treatment and auricular acupuncture as treatments for depression (40). Consistently, in the present study, the patients who received taVNS treatment showed lower SDS scores compared with the control patients, indicating that taVNS effectively improved the depression symptoms of alcohol-dependent patients after withdrawal.

taVNS has shown promising effectiveness in treating primary insomnia (41). Another clinical study confirmed that taVNS can alleviate insomnia in patients with depression (42). In line with these results, the PSQI scores were significantly lower in the treatment group than in the control group, providing more data for taVNS to improve sleep quality in alcohol-dependent patients.

Studies on the effects of taVNS on anxiety are limited and controversial. taVNS has been shown to be effective in treating anxiety symptoms in depressed patients (42). However, taVNS has been reported to not affect the generalization and physiological indices of fear, a typical hallmark of anxiety disorders (43). The results of the present study first confirmed that taVNS had no significant effect on anxiety symptoms in patients with alcohol dependence. Similarly, there was no difference in the craving scores between the two groups. Numerous studies have demonstrated that anxiety is widely considered to be causally related to alcohol craving and consumption, as well as the development and maintenance of alcohol use disorder (44). Thus, it is rational to presume that the lack of effect of taVNS on craving may be related to the fact that taVNS does not significantly improve anxiety in alcohol-dependent patients.

Recent animal studies have explored the effects of taVNS on the BDNF levels. Notably, taVNS has been shown to induce neuroprotection against cerebral ischemia/reperfusion injury, which might be related to the upregulation of BDNF expression in the ischemic cortex (45). Consistently, the mean BDNF levels were significantly higher in the patients who received taVNS treatment than in control patients. It is known that BDNF levels are generally decreased in depressive patients and can be increased by antidepressant therapies (46). Correlation analysis showed that BDNF levels were negatively correlated with the 24-item Hamilton Rating Scale for Depression (HAMD-24) scores in elderly patients with refractory depression after repetitive transcranial magnetic stimulation (rTMS), suggesting that rTMS might improve depression by influencing peripheral BDNF levels (47). Similarly, peripheral BDNF concentrations were higher in patients with sleep disorders, and multiple linear regression analysis revealed that peripheral BDNF concentrations were independently correlated with PSQI scores (48). These findings indicate that a close relationship between BDNF, depression (49), and sleep disturbances (50) exists. Taken together, it is rational to deduce that taVNS could alleviate depression symptoms and sleep quality in alcohol-dependent patients after withdrawal, which might be involved in the increased levels of peripheral BDNF.

Plasma and serum BDNF concentrations are both common indicators for evaluating the level of BDNF in peripheral blood (51). Recent studies have consistently reported altered levels of BDNF in the circulation (i.e., serum or plasma) of patients with major depression, bipolar disorder, Alzheimer's disease, Huntington's disease, and Parkinson's disease (52), suggesting that BDNF levels in serum and plasma can be used to reflect the level of BDNF in peripheral blood. Moreover, it has been suggested that plasma BDNF levels are significantly positively correlated with cerebral spinal fluid BDNF levels, which indicates that plasma BDNF levels might represent the BDNF expression profile of the central nervous system (53, 54). Furthermore, a meta-analysis of 52 studies indicates that peripheral BDNF level, better documented in plasma than in serum, is a potential biomarker of disease activity in bipolar disorder (55). Therefore, plasma BDNF levels were selected in the present study.

Several lines of evidence suggest an anti-inflammatory effect of taVNS. First, animal studies have suggested that taVNS could suppress proinflammatory cytokine levels and NF-κB p65 expression in the lung tissues in endotoxemia-affected anesthetized rats (56). Second, clinical evidence has indicated that VNS is associated with marked peripheral increases in pro- and anti-inflammatory circulating cytokines, such as IL-6, TNF-α, and TGF-β in patients with resistant depression (57). However, the downregulation of inflammatory factor levels by taVNS in alcohol-dependent patients was not observed in the present study. The specific mechanism of this discrepancy is not clear, which may be partly due to the different types of diseases.

Although preclinical studies have indicated decreased serum leptin concentrations in normally fed rats (58) and high-fat

diet-fed rats (25) that received VNS, there are no reports on clinical studies on the effect of VNS on peripheral leptin levels. Considering that there is a close relationship between blood leptin levels and alcohol craving, we first investigated the plasma leptin concentrations in alcohol-dependent patients after taVNS treatment. Similar to the effect on alcohol craving, taVNS did not change the levels of leptin, indicating that taVNS may not be suitable as a treatment for craving after withdrawal in alcohol-dependent patients.

There are some limitations to this study. First, the current study is a single-center study with a small sample size. Second, the scale scores of the patients were collected only before and after the 4-week treatment. It is more appropriate to collect the scale score information once a week. Third, since benzodiazepine substitution may affect the levels of BDNF (59, 60), the changes in BDNF levels before and after treatment with benzodiazepine should be observed. Fourth, the long-term effects of taVNS on the plasma levels of BDNF, IL-6, TNF-α, and leptin were not observed.

At the end of this study, we concluded that taVNS could improve depression symptoms and sleep quality in alcohol-dependent patients after withdrawal, which might be related to the upregulation of plasma BDNF levels. Further investigation will help identify the exact mechanism of the potential therapeutic benefits of taVNS on PAWS in alcohol-dependent patients after withdrawal.

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 Hefei Fourth People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-MW, Y-YX, YZ, and L-YX participated in the experimental design and statistical analyses. YZ, Q-QW, WH, YL, and Y-HS performed the experiments. Y-MW and Y-YX drafted the manuscript. Y-YX edited the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Severe Encephalatrophy and Related Disorders From Long-Term Ketamine Abuse: A Case Report and Literature Review

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Ketamine is a glutamate N-methyl D-aspartate receptor antagonist and an anaesthetic agent that has been effectively used to treat depression. However, ketamine has also been increasingly used for recreational purposes. The dissociative side-effects of ketamine use, such as hallucinations, are the reason for abuse. Additionally, long-term ketamine abuse has been highly associated with liver-gallbladder and urinary symptoms. The present study reports the case of a **28-year-old young male adult** with an 8-year history of daily inhalation of ketamine. We investigated the association between ketamine abuse and the mechanism of its adverse effects, particularly encephalatrophy, and attempted to find a link between these disorders. These results would help us to better understand ketamine usage, ketamine abuse effects and the addictive mechanism. To the best of our knowledge, the present case is the first report of severe brain atrophy related to ketamine abuse. Details of the patient are presented and the mechanism of the encephalatropy-associated ketamine abuse is discussed. Furthermore, organ dysfunction following chronic ketamine abuse may indicate that the side effects are the result of comprehensive action on multiple regions in the brain.

Keywords: ketamine, abuse, encephalatrophy, disorder, mental activity

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INTRODUCTION

Ketamine is a derivative of phencyclidine that was first successfully synthesised by the American pharmacist Calvin Stevens in 1962. Ketamine was initially used as an effective veterinary anaesthetic. Then, it became commercially available for human use as a rapid-acting intravenous anaesthetic. However, the adverse side-effects were quickly realised and its use in treatment was reduced. Great importance has been attached to ketamine again with the increased number of patients with a depressive disorder and with the rapid-acting (within hours) and sustained (lasting up to 7 days) antidepressant effects of ketamine in traditional anti-depressant drug-resistant patients (1, 2), and it has been demonstrated that such effects may be associated with an opioid effect (3). Additionally, experiments have demonstrated that ketamine use can reduce suicidal ideation rapidly (4–6), while that effects on suicidal ideation are partially independent of its effects on mood (7). The therapeutic action on both depression and suicidal behaviour may be highly significantly correlated to some microRNAs (8).

Patients who abuse ketamine develop non-specific clinical symptoms (9), particularly neuropsychiatric symptoms. Liver-gallbladder symptoms, such as cholestasis, biliary dilatation or abnormal liver function, and urinary symptoms, such as increased frequency, hydronephrosis, chronic kidney injury and renal failure have also been reported (10–15). Ketamine may also cause sclerosing cholangitis in patients with COVID-19 (16). In addition, Cheng-Chung Liu has reported pulseless ventricular tachycardia associated with ketamine abuse (17). In the present case report, a patient with an 8-year history of daily inhalation of ketamine developed brain atrophy. Although ketamine addicts with neuropsychiatric symptoms have been described, such a patient with severe encephalatrophy has not been reported. To the best of our knowledge, the present case is the first report of severe encephalatrophy related to ketamine abuse. Written informed consent was obtained from the family of the patient.

CASE DESCRIPTION

A 28-year-old male was admitted to the respiratory department of Jian'ou Hospital (Fujian, China) with repeated coughing and yellow phlegm in 2018. Family members complained that the patient had a history of ketamine abuse of about five to seven times monthly for 8 years. The last ketamine inhalation was the day before he was admitted to the hospital, **according to a family member.** During the past 5 years, he had been experiencing weakness of the lower limbs, numbness, sensory disorder, decreased muscle strength, difficulty climbing stairs, recurrent frequent urination and urgency and pain during urination. These symptoms persisted and were not significantly relieved by several conservative treatments but were worsened by repeated convulsions, aching in the hepatic region and jaundice 2 years ago. Then, he was diagnosed with "autoimmune hepatitis, chronic cholecystitis and cholangitis." **At that time,** a craniocerebral computed tomography (CT) scan revealed a widened and deepened cerebral sulcus, the cerebral palsy became flattened, the ventricles expanded, the cerebellum was thickened, and brain volume decreased (**Figure 1**). Electromyography revealed a central motor and sensory conduction disorder, and the motor nerve conduction velocity of bilateral tibial nerves was slower, indicating ketamine-related brain atrophy. His liver function normalised completely after dexamethasone treatment **(15 mg for treatment and 5 mg for maintenance for more than 3 months). The patient planned to have cholecystectomy surgery 1 year later, but the operation was cancelled due to abnormal liver function and the development of renal failure.** A CT examination revealed a constricted bladder with dilatation of the bilateral upper urinary tract, moderate hydronephrosis and medullary sponge kidney with multiple renal papillary calcifications. Subsequently, the patient's urine volume decreased gradually until he was not producing urine. He underwent haemodialysis treatment twice per week. After a sudden fall about 2 months before this hospitalisation, the patient was unable to walk and was confined to a wheelchair. He could not speak but made some slurred sounds, and he was conscious 2 weeks before admission.

The patient and his family members denied a history of cerebral disease or alcohol abuse. He was somnolent and jaundiced at admission. A physical examination revealed that muscle strength of both lower limbs was 0 and that of the upper limbs was 3. Routine blood testing revealed an increase in the number of leukocytes and a decrease in the number of erythrocytes. The haemoglobin value was 65 g/l. A faecal occult blood test was positive at 3+. His liver function tests (LFTs) were abnormal (serum bilirubin 283.3 mol/L, alkaline phosphatase 1,804 IU/L, alanine transaminase 19 IU/L, yGT 762 IU/L, and albumin 28.2 g/dL). Other blood tests revealed renal failure (urea 26.97 mmol/L and creatinine 375 μmol) and myocardial failure (NT-pro BNP >35,000 ng/L). Cerebrospinal fluid (CSF) was tested three times, but the routine test, culture test, and syphilis test were all negative. A chest and abdominal CT scan demonstrated pneumonia and bilateral kidney abnormalities. The patient's condition deteriorated rapidly with regular pneumonia, blood transfusions and haemodialysis treatments. During treatment, he presented with sweating, clammy limbs and repeated convulsions. Then, he required intensive care support. Symptoms improved initially with symptomatic treatment, but worsened quickly, accompanied by dyspnoea and purple lips. After convulsing again, the patient slipped into a deep coma and was intubated and maintained on a ventilator. In the end, he died from brain damage and dysfunction with other multiple organ dysfunctions.

DISCUSSION

Ketamine is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist commonly used initially as a human intravenous anaesthetic. However, its use has decreased due to side effects, particularly addiction. Ketamine addiction is related to the interference of glutamate neurotransmission, which influences the establishment of the subcortical regions, such as nucleus accumbens, which is associated with addictive behaviours (18). Studies also show that there are specific antidepressant properties of glutamatergic medications targeting NMDA receptors (19, 20) and effective reduction of suicidal ideation (5). Furthermore, a small dose of ketamine can relieve pain in advanced tumour patients (14, 21, 22), but side effects must be considered. The side-effects of ketamine abuse or misuse (23), except addiction, include neurotoxicity, cognitive dysfunction, adverse events associated with mental status, psychotomimetic effects, uropathy effects, liver-gallbladder effects and cardiovascular events. **Research has shown that chronic ketamine use may lead to brain atrophy, particularly during the time of brain development (24, 25), and the anti-depressive effects may be associated with increases in brain area volume (20). But to our knowledge, we are the first to report a young adult suffering from severe brain atrophy after long-term abuse of ketamine**.

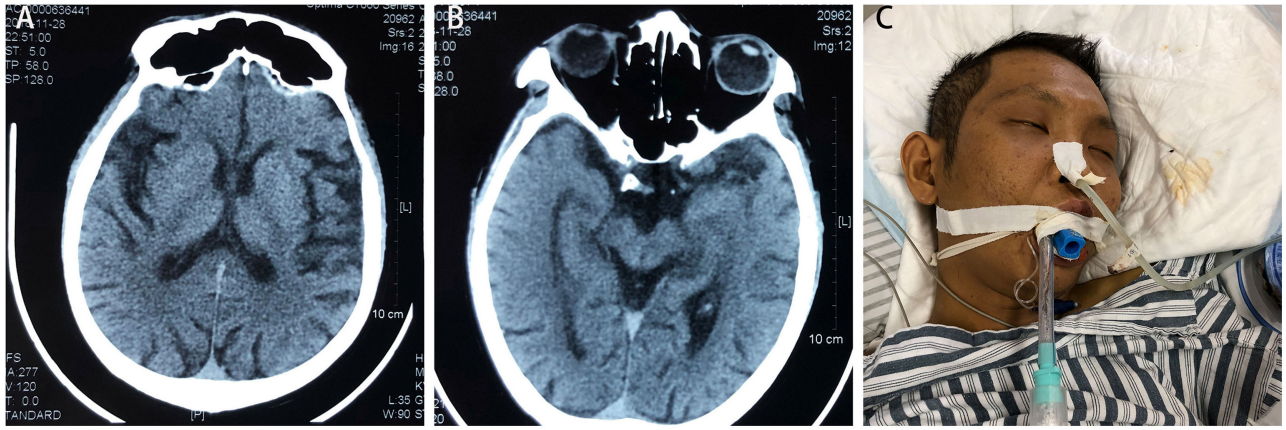

FIGURE 1 | Craniocerebral computed tomography scan indicates wide and deep cerebral sulcus, flattened cerebral palsy, expanded ventricles, thickened cerebellum and reduced brain volume **(A,B)**. **(C)** The patient was placed on a ventilator but soon died of persistent epilepsy and multiple organ failure.

The side effects of ketamine abuse or misuse are commonly seen. In our case, the patient was diagnosed with autoimmune hepatitis, chronic cholecystitis, cholangitis and renal failure. It is unknown why he first presented with neurological symptoms from the weakness of the lower limbs, numbness, sensory disorder and decreased muscle strength. He then repeatedly convulsed, suddenly lost the ability to speak and died of brain dysfunction. Symptoms, such as weakness of the lower limbs and aphasia (26, 27), indicate brain damage or brain functioning zone damage, but his brain atrophy may not be the same as common degeneration (28) which is associated with ageing. No signs of intracranial infection or any other brain disease were detected on CSF tests, such as cerebral infarction from the CT scans, except atrophy. However, a patient with status epilepticus reportedly also developed brain atrophy and some similar neurological symptoms after using ketamine (29). Therefore, it is likely that brain atrophy is a side-effect of chronic ketamine use. However, because ketamine is a dissociative drug, it is trivial for physicians to determine that a patient may appear with neuropsychiatric symptoms while overlooking a brain image to check whether any degenerative brain changes are occurring at the same time. **This could be due to the few reports of brain atrophy associated with ketamine usage (24, 25).**

There are several subtypes of encephalatrophy also known as brain atrophy, and it can be diagnosed by CT scan (30). As people age, it is common to see brain atrophy, and in recent years, many studies have demonstrated that brain atrophy is associated with dementia or Alzheimer's disease (31). However, most surveys have focused on the relationship between brain atrophy and cognitive dysfunction and have found that brain atrophy leads to cognitive dysfunction (32–34). **No study has investigated the sensory or motor symptoms related to brain atrophy**. As our patient was very young and his symptoms were unique, such as loss of speaking ability and repeated convulsions, we infer that the brain atrophy in a ketamine addict may not be the same as common degeneration, as the patient may also have damage to specific brain functioning zones. **Additionally, a reduction in frontal grey matter volume can be detected by MRI among long-term ketamine users (35); therefore, it was reasonable for us to find brain atrophy on CT in our case.**

Other lower affinity pharmacological targets of ketamine include, but are not limited to, γ-aminobutyric acid (GABA), dopamine, serotonin, sigma, opioids and cholinergic receptors, as well as voltage-gated sodium and hyperpolarisation-activated cyclic nucleotide-gated channels (1, 9). These may lead to diverse effects with chronic ketamine use. For example, GABA is the principal inhibitory neurotransmitter in the adult brain, and the balance between inhibitory and excitatory synaptic transmission is essential for normal neuronal communication and brain function. Several neurodevelopmental diseases have been associated with the GABAergic system during brain development (36) by impairing the integration of GABAergic neurons in the cerebral cortex. However, the impact on the adult brain is unknown. **In our case, the patient presented with convulsions, which may have been the result of inadequate inhibitory effects, such as GABA, but** the functional relevance of the actions of ketamine on $GABA_A$ receptors is unclear (9). **A recent study (37) reported that a single subanaesthetic dose of ketamine for a rapid and sustained anti-depressive effect is the result of the action of GluN2B-NMDARs on GABA interneurons, indicating that ketamine may not act directly on other receptors (except NMDA receptors) but includes indirect effects. Additionally, the abusive dose of the drug is similar to that for treatment purposes or even higher** [doses used for recreational ketamine use may range between 1 and 2 mg/kg (i.v.), 50 and 150 mg (i.m.), 100 and 500 mg (oral) or 30 and 400 mg (intranasal insufflation) (38, 39)], **which increases the addiction risk. However, the dose-effects on ketamine receptors are notable.**

It is well-established that ketamine abuse can be neurotoxic, resulting in cognitive impairment and psychotic states (40). Additionally, it was found to be associated with certain receptors. A related study (41) suggested that ketamine neurotoxicity of the brain may occur due to activation of apoptotic pathways in the prefrontal cortex. Another hypothesis (42) of ketamine neurotoxicity is associated with AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors. Furthermore, a survey revealed that changes in membrane AMPA receptors and synaptic function induced by ketamine are mediated by abnormal phosphorylation of the tau protein at specific sites (43). The mechanism of ketamine neurotoxicity remains unclear. A case reported that a woman with major depressive disorder used long-term increasing doses of ketamine from 50 mg/week to 2 g/d for an anti-depression response (44); the woman eventually became a ketamine addict accompanied by loss of consciousness, dissociative immobility and amnesia. This indicates that ketamine is a double-edged sword and that neurotoxicity may be associated with dose. More treatment-related receptors work at low doses, whereas overdoses cause activities of some receptors, such as AMPA, to be modified or damaged, leading to adverse events related to neurotoxicity. As our patient slipped into a deep coma, we confirmed that he was neurotoxic. It is unknown whether the encephalatrophy of our patient was related to ketamine neurotoxicity. More studies on the association between different receptors and doses are needed.

An association has been found between addictive drugs and brain volumetric changes. One case reported that the recreational use of N_2O for 5 months led to encephalatrophy and cognitive dysfunction (45), and the patient's symptoms including encephalatrophy improved after treatment. Furthermore, brain volumetric changes are also observed among other addicts, besides those abusing ketamine (46), such as methamphetamine abusers (47) [and methamphetamine at abstinence (48)] and alcoholics (49, 50) [and alcohol abstinence (51)]. The mechanisms are unknown but may be associated with microRNA (52), glucose metabolism (53) or some brain receptors (54). However, the brain damage would improve after abstinence. In our case, infectious factors were excluded due to the three negative CSF results. His encephalography was associated with ketamine use, as he was a young man without a cerebral disease history. Ketamine has a direct negative inotropic effect and an indirect stimulatory effect due to activation of the sympathetic system by blocking nicotinic acetylcholine receptors located on cerebral perivascular sympathetic nerves, resulting in diminished neurogenic vasodilation and normal blood flow to the brainstem (55), which may explain the patient's encephalatrophy. The patient was anaemic, which was discovered after the brain atrophy, but the anaemia could not explain such severe encephalatrophy.

Our patient also developed renal failure and some other diseases, which may have been related to his brain atrophy. It has been reported that levels of methylguanidine and guanidinosuccinate increase in uraemic patients, which is related to symptoms of convulsions and brain atrophy (56, 57). The patient's renal function tests showed that creatinine and blood urea nitrogen were not significantly elevated with regular haemodialysis treatment, **and brain atrophy was observed before renal failure. Thus, we excluded the possibility of renal-mediated brain atrophy.** The LFTs normalised after the administration of **dexamethasone**. What's more, with a negative liver-related **auto-antibody test on the last admission,** we inferred that **the autoimmune hepatitis was treated properly. However, the patient also presented with abnormal liver function during the last admission, which may have been a result of ketamine or chronic cholecystitis and cholangitis. Ketamine causes liver damage (13, 58, 59). As we are unsure when the abnormal live function and brain atrophy began, the brain atrophy may have been liver mediated. However, as the liver symptoms lasted a short time and were treated quickly, it is unlikely that such severe brain atrophy was caused by abnormal liver function.** We infer that the severity of the brain atrophy may not be related to abnormal renal and liver function. **Additionally, the patient did not have a long history of using some drugs except dexamethasone more than 3 months. Dexamethasone may lead to reduced brain size (60). However, dexamethasone was used after the patient was found to have severe brain atrophy. Thus, we excluded other drug-mediated brain atrophy.**

It is difficult to confirm the mechanism of these non-specific symptoms, and the factors associated with the severity of brain dysfunction. Several hypotheses for the potential relationship between ketamine abuse and urinary tract or liver-gallbladder damage have been proposed. Among these, most theories involve ketamine acting through receptors on the liver-gallbladder or urinary tract, as ketamine is metabolised in the liver by microsomal cytochrome enzymes and the metabolites are excreted into the urine and bile. An animal study (61) showed that injecting NMDA into the dorsal motor nucleus of the vagus increases gallbladder motility and its effect can be abolished by administering ketamine, which explains the relevant gallbladder symptoms. Therefore, it is plausible that the various symptoms of different organs reflect brain damage through organ axes of the central nervous system. That scenario corresponds with our patient's present brain damage followed by dysfunction of other organs.

In conclusion, this is the first report of long-term ketamine use associated with severe encephalatrophy and other neurological symptoms. The mechanism of ketamine side- effects may be the result of comprehensive action of multiple receptors associated with the dose, and the various symptoms may result from organ axes of the central nervous system by some receptors and related miRNA changes. We suggest that brain atrophy be regarded as a common side-effect and that a brain examination should be performed on ketamine addicts. We could observe early receptor-relevant protein changes from visual cerebral volumes changes to have a better understanding of the mechanism of action of ketamine, its side effects, or even prevent the adverse events from progressing. More studies are needed on the ketamine mechanism between receptors and molecules.

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 Fujian Provincial Hospital. The patients/participants provided their written informed consent to participate in this study. Ethical review and approval was not required for the animal study because no animal included in the 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

LL wrote the first draught of the manuscript. YL and RZ treated the patient. HH created the image and collected the clinical information. WW and YW edited the paper and sponsored the study. All authors contributed to the article and approved the submitted version.

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The Influence of Online Game Behaviors on the Emotional State and Executive Function of College Students in China

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Background and Objective: Since the classification of gaming disorder (GD) by the World Health Organization (WHO) as "mental disorder caused by addictive behaviors," there has been controversy regarding whether online game behaviors can lead to mental disorder. This study aims to clarify the correlation between the online game behaviors of college students and anxiety, depression, and executive function of college students in China, from a questionnaire-based investigation.

Methods: Based on the whole class random sampling method, a questionnaire survey was conducted among college students in Northern Anhui, China from March 7 to March 27, 2020. The questionnaires included the Internet Game Addiction (IGA) Scale, Behavior Rating Inventory of Executive Function (Adult Version, BRIEF-A), Generalized Anxiety Disorder Scale (GAD-7) and Patient Health Questionnaire Scale (PHQ-9).

Results: A total of 850 participants completed the survey, including 353 males (41.53%) and 497 females (58.47%). The primary age group was 18–27 years (91.53%), and the educational background was a bachelor's degree (94.7%). The study found that the online behavior of 17.76% of college students was online game behavior. This study did not identify any students who met the criteria for IGA, and 3% met the criteria for indulgent behavior. A dual role of online games was identified; moderate online game activities can improve the emotional state and executive function of college students, while excessive online game behaviors that may not reach the degree of addiction can also harm emotional state and executive function.

Conclusions: This study suggests that although IGA has been regarded as a mental disease, online game behavior should be treated differently. Online game activities should not be entirely denied, but mental disorders caused by excessive gaming activities deserve attention. In particular, the emotional state and executive function of students with excessive online game behaviors should be monitored and intervened in advance to avoid game behaviors turning into indulgent behaviors or addiction. As a cognitive control process, executive function may play a key role in regulating IGA and emotional state.

Keywords: Internet Game Addiction, executive function, anxiety, depression, college students

INTRODUCTION

With the rapid growth of the online game market, many young men indulge in online games, which has resulted in lots of negative social effects. Problems related to IGA have become increasingly concerning. Previous research reported that the prevalence of IGA has been estimated to be 0.5–6% (1, 2). Long et al. (3) analyzed 36 representative investigations and found that the prevalence of problematic IGA was 3.5–17%. King et al. investigated more than 3,000 subjects and found that the prevalence of IGA was 0.3–4.9% (4). In addition, the above studies have found that young people are the high incidence population of IGA. The individual susceptibility constituted by genetic, physio genesis and personality characteristics may predispose young people to addictive tendencies and indicates that IGA disorder of young people is a real problem that needs attention.

IGA has been considered as a clinical phenomenon that requires further study, per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2013 (DSM-5) (5). In 2019, the World Health Organization (WHO) regarded gaming disorder as a mental disease and classified it in the category of the disorders caused by addictive behaviors (6). The introduction of two new standards has guided the primary direction for research in this field (7), but has also generated significant controversy. Clinical studies have found that IGA has the characteristic similar to those of behavioral addiction, such as excessive attention-seeking, compulsive, lack of control and impulsive behavior (8). Related research has indicated that IGA may decrease sleep quality and has a strong correlation with different degrees of anxiety, depression and other psychological distress (9, 10). However, some researchers have suggested that IGA should not be classified as a mental disease (11). It has been reported that online games bring happiness to players, reduce anxiety, depression (12) and improve cognitive function (13). In addition, most online gamers are not exposed to addiction, suggesting the presence of factors mitigating against IGA. Previous studies highlighted that executive function plays a key role in the regulation of addictive behaviors and emotional status (14). Executive function includes decision-making, planning, inhibition and behavioral shift (15). Moreover, executive function can prevent the development of addiction by inhibiting impulsive and controlling behaviors, whilst degradation of executive function leads to an increase in impulsive behaviors and addiction development (16). Meanwhile, excessive online gaming could be detrimental to executive function, consequently spiraling without control and leading to impulsive behaviors (17). In essence, executive function plays a key role in IGA mitigation and mental health.

This study focused on the roles of executive function, anxiety and depression on the development of IGA, based on the Behavior Rating Inventory of Executive Function (Adult Version, BRIEF-A), Generalized Anxiety Disorder Scale (GAD-7) and Patient Health Questionnaire Scale (PHQ-9). Since online gamer demographics are predominantly individuals in the younger age-bracket, college students were selected for becoming participants of this study. This investigation sheds further light on the correlation of IGA and emotional disorder with executive function disorder, thus providing references to IGA mitigation within clinical practice.

METHOD

Research Subjects

Based on the whole class random sampling method, a questionnaire survey was conducted on college students in Northern Anhui Province, China from March 7 to March 27, 2020. An online questionnaire survey method was used for the study and more than two classes were randomly selected from each grade of each school. With the help of school counselors, questionnaire links were distributed in a QQ group or WeChat group, and only one questionnaire could be completed per IP address. Questionnaires that were completed too quickly were eliminated and 850 valid questionnaires were finally considered for the study. Bengbu Medical College Institutional Review Board authorized this study (approval number: 2019-199). All experiments were performed in compliance with the regulatory approval.

Research Tools

IGA Scale

Currently, there are few measurement tools for the diagnosis and evaluation of IGA which are based on DSM-5 and ICD-11. However, there are several inconsistencies between the two criteria used for determining the prevalence of IGA (7), which in turn, leads to a significant difference in determining the incidence of IGA. The development of measurement tools needs to be validated in cross-cultural clinical samples for effectiveness and reliability. Better results would be obtained if objective indicators including autonomic nervous system response, and electrophysiological parameters can be measured (5, 18, 19). Based on the above reasons, the IGA scale was used in this study. The IGA scale was compiled by Chinese scholars, which used Chinese college students as samples and adopted an event-related brain potential method to identify objective electrophysiological indexes that could distinguish IGA users from other Internet users. The reliability and stability of the scale for Chinese young people have been proven by reliability and validity tests (20, 21).

IGA scale with 11 questions and a Likert 5-point scoring method were used for the study. From being "highly consistent" to "very inconsistent," the consistency between the actual situation of the subjects and the questionnaire items were correspondingly scored from "4 points" to "0 points," respectively. Subjects with higher scores were more likely to develop IGA. A score < 20 was regarded as normal online game behavior, a score ≥ 20 but <30 was regarded as online game indulgent and a score ≥ 30 was considered as IGA. In this study, the Internal consistency Cronbach's α of the questionnaire was 0.856, and the KMO test coefficient (Bartlett's test, $P < 0.05$) was 0.828, indicating that the scale had good reliability and validity.

The Generalized Anxiety Disorder Scale

The Generalized Anxiety Disorder Scale (GAD-7) was previously translated into Chinese and validated by researchers in China (22). GAD-7 is a quantitative evaluation standard recommended by DSM-5 published by the American Psychiatric Association. It is an effective tool to identify possible cases with generalized anxiety disorder and has shown good reliability and validity in previous studies. The score is divided into four levels: 0–4, 5–9, 10–14, and 15–21, corresponding to no, mild, moderate and severe anxiety, respectively (23). In this study, the Cronbach's α of the standardized item of the scale was 0.922, and the KMO test coefficient (Bartlett's test, $P < 0.05$) was 0.920, indicating that the scale had good reliability and validity.

Patient Health Questionnaire Scale

The Patient Health Questionnaire Scale (PHQ-9) was previously translated into Chinese and validated by researchers in China (24, 25). PHQ-9 is based on nine criteria of depression as stated in DSM-5 and is highly sensitive to depressive symptoms. The score is divided into five levels: 0–4, 5–9, 10–14, 15–19, and 20–27 corresponding to no, mild, moderate, moderately-severe and severe anxiety, respectively (26). In this study, the Cronbach's α of the standardized item of the scale was 0.905, and the KMO test coefficient (Bartlett's test, $P < 0.05$) was 0.930, indicating that the scale had good reliability and validity.

Executive Function Scale

Executive function was measured with the Chinese version Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) developed by Roth and Gioia (27), It contains 75-items that yield an overall score, the Global Executive Composite(GEC), which is derived from two index scores [Behavioral Regulation Index (BRI) and Metacognitive Index (MI)]. The BRI is comprised of four clinical scales: Inhibit, Shift, Emotional Control and Self-Monitor. The MI is comprised of five clinical scales: Initiate, Working Memory, Plan or Organize, Task Monitor and Organization of Materials. A 1–3 level scoring system was adopted, with a score of 1 for "never," a score of 2 for "sometimes" and a score of 3 for "often." The higher the total score, the more serious the impairment of executive function. In this study, the internal consistency Cronbach's α of this scale was 0.976, and the KMO test coefficient (Bartlett's test, $P < 0.05$) was 0.966, indicating that the scale had good reliability and validity.

Statistical Analysis

The SPSS 25.0 software was used for statistical analysis in this study. The measured data were expressed as (M ± SD), and the independent sample *t*-test was used to compare two groups of measured data. The measured data for multiple groups were analyzed by one-way ANOVA, and multiple comparisons were made. Also, correlation analyses and multiple linear regressions were used to identify the relationships between the IGA score and anxiety, depression, and executive function, with a test level α of 0.05.

TABLE 1 | General demographic data of subjects ($n = 850$).

	Variables	Number	Percentage (%)
Total		850	100
Gender	Male	353	41.53
	Female	497	58.47
Age	<18	34	4.00
	18–23	677	79.65
	24–27	101	11.88
	>27	38	4.47
Grade	Freshman	200	23.53
	Sophomore	98	11.53
	Sophomore	287	33.76
	Junior	180	21.18
	Senior	40	4.71
	Postgraduate or above	45	5.30
Residence	Country	363	42.71
	Town	195	22.94
	City	292	34.35

RESULTS

General Demographic Data of Subjects

A total of 850 participants completed the survey, including 353 males (41.53%) and 497 females (58.47%). The overall age distribution was between 18 and 27 years (91.53%). The educational background of the subjects mostly comprised a bachelor's degree (94.7%). Other general demographic data are shown in **Table 1**.

Network Usage of Subjects

Primary Internet Behaviors of Subjects Over the Past 12-Month Period

The 850 participants of the study were divided into two groups according to their primary Internet behaviors over the past 12 months. There were 151 (17.76%) participants in the Game group and the primary Internet behavior was playing online games. There were 699 (82.24%) participants in the Non-game group and the primary Internet behaviors included watching cinematographic and television programs, short videos, reading online novels, and shopping (**Figure 1**).

Basic Information of the Game and Non-game Groups

There were significant differences in gender, grade, and online time between the Game and Non-game groups (**Table 2**).

Relationships Between IGA Scores and Anxiety, Depression, and Executive Function Scores

Differences in Anxiety and Depression Levels Among Groups

Based on the IGA score, the Game group was further divided into a 0–9 score group (6.68 ± 2.16), a 10–19 score group (14.84 ± 2.24), and a 20–29 score group (22.65 ± 1.98). The results showed

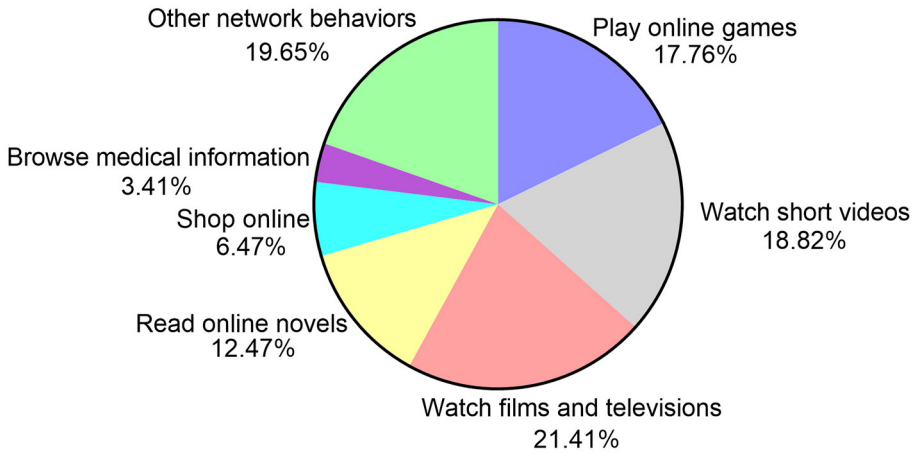

FIGURE 1 | The primary network behaviors and grouping of participants ($n = 850$) over the past 12 months.

TABLE 2 | Basic information of the game group and the Non-game group.

	Variables	Network usage type		χ^2	*P*
		Non-game ($n = 699$)	Game ($n = 151$)		
Gender	Male	254 (36.3%)	99 (65.6%)	43.678	0.000***
	Female	445 (63.7%)	52 (34.4%)		
Age	<18	25 (3.6%)	9 (6.0%)	2.122	0.548
	18–23	557 (79.7%)	120 (79.5%)		
	24–27	85 (12.2%)	16 (10.6%)		
	>27	32 (4.6%)	6 (4.0%)		
Grade	Freshman	146 (20.9%)	54 (35.8%)	15.774	0.008**
	Sophomore	84 (12.0%)	14 (9.3%)		
	Sophomore	245 (35.1%)	42 (27.8%)		
	Junior	154 (22.0%)	26 (17.2%)		
	Senior	33 (4.7%)	7 (4.6%)		
	Postgraduate or above	37 (5.3%)	8 (5.3%)		
Residence	Country	298 (42.6%)	65 (43.0%)	1.822	0.402
	Town	155 (22.2%)	40 (26.5%)		
	City	246 (35.2%)	46 (30.5%)		
Online time	<1 h	27 (3.9%)	17 (11.3%)	17.305	0.002**
	1–2 h	77 (11.0%)	13 (8.6%)		
	2–4 h	199 (28.5%)	33 (21.9%)		
	4–8 h	265 (37.9%)	53 (35.1%)		
	>8 h	131 (18.7%)	35 (23.2%)		

$^{**}P < 0.01$, $^{***}P < 0.001$.

that subjects without depression or anxiety accounted for the most significant proportion of the 0–9 score group, and subjects with more than moderate anxiety or depression accounted for the most significant proportion of the 20–29 score group (**Figure 2**).

Scores of Anxiety and Depression, the Executive Function Total Scores, and the Executive Function Score of Each Factor Among Groups

The results showed that students in the 0–9 score group (based on the IGA score) had lower scores on the anxiety, depression, and executive function scales than those in the Non-game group, 10–19 score group, and 20–29 score group ($P < 0.05$). However, students who were in the 20–29 score group had higher scores on the anxiety, depression, and executive function scales than those in other groups ($P < 0.05$) (see **Table 3**). These trends are shown in **Figure 3**.

Correlation Analysis of IGA Scores With Gender, Age, Anxiety, Depression, and Executive Function

Table 4 shows the correlation between IGA scores and gender, age, anxiety, depression, and executive function. The results showed that IGA scores were positively correlated with age, anxiety, depression, executive function, and executive function subscale factors (see **Table 4**).

Multiple Linear Regression Analysis of IGA Scores With Age, Anxiety, Depression, and the Total Score of Executive Function ($n = 151$)

The IGA score was treated as the dependent variable, and age, anxiety, depression, and executive function scores were treated as independent variables for multiple linear regression analysis. The Variance Inflation Factor (VIF) for the predictor variables ranged from 1.027 to 4.768, which is acceptable as being below the threshold of 10; likewise, Tolerance levels for each predictor ranged from 0.210 to 0.974, which is also a satisfactory range. The results indicated that age, anxiety, and the total score of executive function were independent influencing factors of online game behavior (see **Table 5**).

DISCUSSION

This study investigated the differences in anxiety, depression, and executive function scores among the Non-game group and the Game group (the Game group was divided into the 0–9, 10–19, 20–29 score groups according to the IGA scale score). The results showed that the scores for anxiety, depression, and executive function of subjects in the 0–9 score group were lower than those in the Non-game group, 10–19 score group,

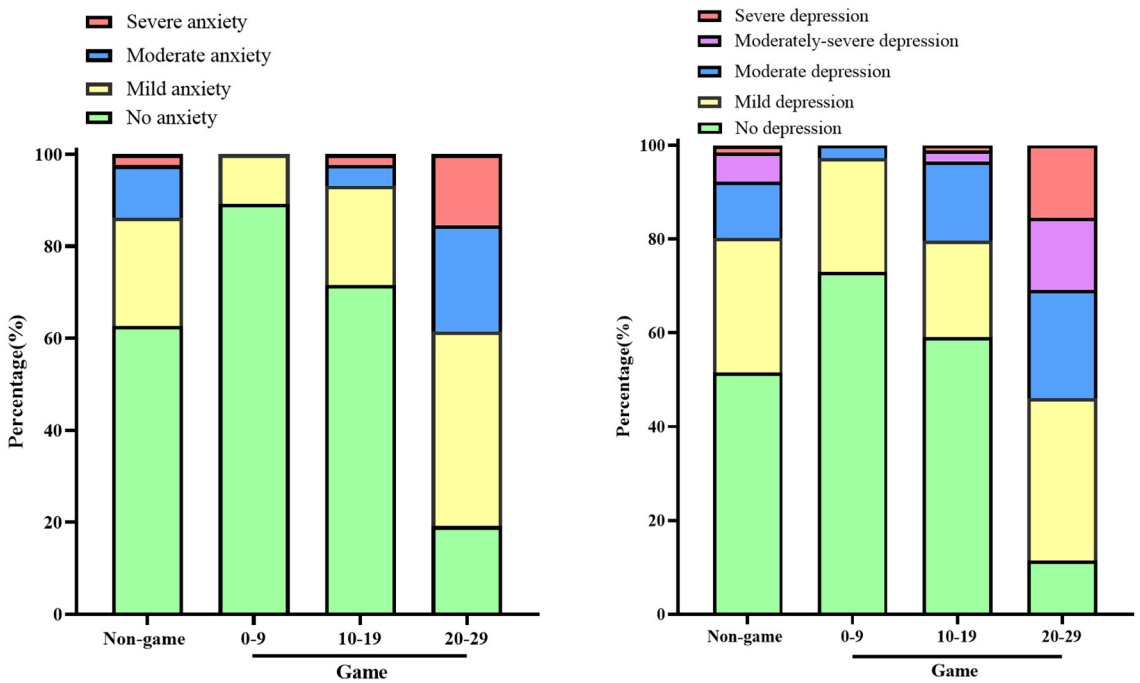

FIGURE 2 | Different anxiety levels (GAD-7) and depression levels (PHQ-9) among groups without depression or anxiety accounted for the most significant proportion in the 0-9 score group, and subjects with more than moderate anxiety or depression accounted for the most significant proportion in the 20–29 score group. 0–9, 10–19, 20–29, respectively represents group whose scores of Internet Game Addiction Scale were 0–9, 10–19, 20–29.

TABLE 3 | Scores of anxiety and depression, total scores, and the executive function scores of each factor among groups (M ± SD).

	Non-game[a] (*n* = 699)	Game			*F*	*P*	*Post-hoc*
		0–9[b] (*n* = 37)	10–19[c] (*n* = 88)	20–29[d] (*n* = 26)			
GAD-7	3.96 ± 4.49	1.00 ± 1.96	2.99 ± 4.11	8.81 ± 5.46	17.382	0.000***	d>c=a>b
PHQ-9	5.50 ± 5.32	2.57 ± 3.29	4.75 ± 5.13	11.92 ± 7.00	17.156	0.000***	d>c=a>b
BRIEF-A	103.07 ± 28.42	83.86 ± 15.68	104.42 ± 28.35	132.69 ± 29.23	15.544	0.000***	d>c=a>b
BRI	43.44 ± 12.66	35.35 ± 5.92	43.47 ± 12.30	57.08 ± 13.14	15.659	0.000***	d>c=a>b
Inhibit	11.61 ± 3.40	9.62 ± 1.75	11.65 ± 3.26	15.15 ± 3.04	14.293	0.000***	d>c=a>b
Shift	8.73 ± 2.80	6.95 ± 1.54	8.83 ± 2.64	11.38 ± 2.83	13.399	0.000***	d>c=a>b
Emotional control	14.50 ± 4.58	11.46 ± 2.12	14.22 ± 4.56	19.42 ± 5.88	15.810	0.000***	d>c=a>b
Self-monitor	8.60 ± 2.79	7.32 ± 1.47	8.77 ± 2.71	11.12 ± 2.66	10.071	0.000***	d>c=a>b
MI	59.63 ± 16.30	48.51 ± 10.28	60.95 ± 16.86	75.62 ± 17.10	14.474	0.000***	d>c=a>b
Initiate	12.51 ± 3.58	10.11 ± 2.00	12.95 ± 3.43	15.27 ± 3.55	11.582	0.000***	d>c=a>b
Working memory	11.90 ± 3.51	9.57 ± 2.27	11.94 ± 3.66	15.58 ± 3.11	15.292	0.000***	d>c=a>b
Plan/organize	14.69 ± 4.44	12.03 ± 3.31	14.94 ± 4.61	19.15 ± 4.70	13.357	0.000***	d>c=a>b
Task monitor	9.02 ± 2.66	7.30 ± 1.35	9.35 ± 2.64	11.23 ± 3.04	11.906	0.000***	d>c=a>b
Organization of materials	11.51 ± 3.42	9.51 ± 2.29	11.76 ± 3.71	14.38 ± 4.54	10.261	0.000***	d>c=a>b

****P < 0.001; GAD-7, The Generalized Anxiety Disorder Scale; PHQ-9, Patient Health Questionnaire Scale; BRIEF-A, Executive Function-Adult Version; BRI, Behavioral Regulation Index; MI, Metacognitive Index.*

and 20–29 score group. It indicated that compared with other online entertainment behaviors, moderate online games might help alleviate anxiety and depression, and improve executive function. This confirms prior research findings that moderate online games can improve players' cognitive executive ability (28, 29) and alleviate or even reduce players' anxiety, depression, and other negative emotions (30, 31). A brain electrophysiology study on games also showed that moderate games activate brain areas related to emotion processing and that the frontal lobe areas related to attention are also more activated (32).

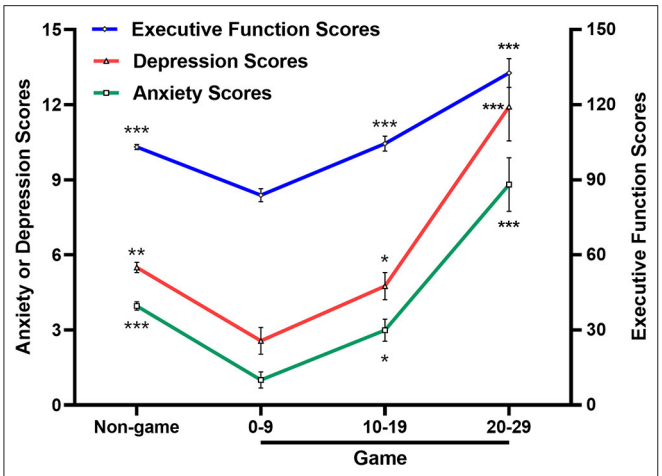

FIGURE 3 | Trends of anxiety, depression, and total scores of executive function among groups. 0–9, 10–19, 20–29, respectively represents group whose scores of Internet Game Addiction Scale were 0–9, 10–19, 20–29; *$P < 0.05$: vs. 0–9 Game group, **$P < 0.01$: vs. 0–9 Game group, ***$P < 0.001$: vs. 0–9 Game group.

However, this study found that the scores for anxiety, depression, and executive function of subjects with higher online game scores (20–29 scores) were significantly higher than those in the 0–9, and 10–19 score groups, and in the Non-game group. Further correlation and regression analyses for the Game group revealed that anxiety, depression, and executive function were significantly positively correlated with the IGA score. The above conclusions showed that although excessive online game behavior (20–29 scores) did not reach the degree of addiction (online game scores were 30 and above), it still had a certain degree of negative impact on the emotions and executive functions of players.

This study showed the correlation of emotion and addiction with executive function. As a key subcortical brain area (e.g., nucleus accumbent, amygdala, cingulum gyrus, hypothalamus), the limbic system is closely related to addiction development (33). Appropriate online gaming leads to increased release of dopamine within the limbic system, resulting in pleasure. Consequently, such gamers feel calm, with anxiety and depression being mitigated (34). Therefore, moderate gaming can maintain emotional volatility in balance, while IGA causes emotional imbalance. In order to pursue pleasure through online games, gaming addicts are unable to extricate themselves from playing, resulting in impulsive and uncontrollable behaviors. Abrupt gaming halts trigger negative emotions such as anxiety, depression and anger (35). At this stage, the purpose of online gaming addicts to compulsively play is not only a method for pleasure-seeking, also a means to offset negative emotions, such as anxiety and depression (36). This also describes why this study found that online gaming abusers have more serious anxiety and depression behavioral traits. Previous studies have found that IGA was significantly associated with anxiety, depression, and alexithymia (37).

Being one of the functions of the frontal cortex (15), executive function is also involved in addiction regulation (38). Indeed,

TABLE 4 | Correlation analysis between online game scale scores and gender, age, anxiety, depression, and executive function ($n = 151$).

	IGA scale	
	r	*P*
Gender	−0.004	0.960
Age	0.176	0.030*
Online time	0.143	0.079
GAD-7	0.556	0.000***
PHQ-9	0.533	0.000***
BRIEF-A	0.570	0.000***
BRI	0.575	0.000***
Inhibit	0.551	0.000***
Shift	0.559	0.000***
Emotional control	0.544	0.000***
Self-monitor	0.503	0.000***
MI	0.543	0.000***
Initiate	0.523	0.000***
Working memory	0.545	0.000***
Plan/organize	0.513	0.000***
Task monitor	0.528	0.000***
Organization of materials	0.449	0.000***

*$P<0.05$, ***$P<0.001$; IGA Scale, Internet Game Addiction Scale; GAD-7, The Generalized Anxiety Disorder Scale; PHQ-9, Patient Health Questionnaire Scale; BRIEF-A, Executive Function-Adult Version; BRI, Behavioral Regulation Index; MI, Metacognitive Index.*

TABLE 5 | Multivariate regression analysis ($n = 151$).

	B	SE	Beta	*t*	*P*
(Constant)	0.726	2.234		0.325	0.746
Age	2.139	0.641	0.213	3.336	0.001**
GAD-7	0.385	0.148	0.324	2.601	0.01*
PHQ-9	−0.053	0.129	−0.06	−0.413	0.68
BRIEF-A	0.075	0.018	0.406	4.151	0.000***

*$P<0.05$, **$P<0.01$, ***$P<0.001$, $R^2 = 0.419$, Adjusted $R^2 = 0.403$; GAD-7, The Generalized Anxiety Disorder Scale; PHQ-9, Patient Health Questionnaire Scale; BRIEF-A, Executive Function-Adult Version.*

executive function does include advanced brain functions, including planning, inhibiting, control, shift and decision-making (39). Executive function mitigates addiction by inhibiting impulse behaviors; normal executive function can maintain online gamer behavior in a moderate state and abate/stabilize emotional volatility. Impaired executive function leads to limbic system dysregulation, thus aggravating impulsive behavior and causing IGA (40). In addition, IGA can consequently aggravate executive function damage. For instance, executive function disorder is observed in online gaming addicts (41) and Studies of brain potentials (42) and functional magnetic resonance (43) have found that IGA causes executive dysfunction through frontal lobe injury.

This is consistent with the conclusion that gaming abusers are exposed to poor executive function. Hence, executive function may play a key role in the mitigation of IGA and regulation of emotional status.

It has been found that age has an inverted U-shaped relationship with GD, the risk peaks in puberty and decreases at ∼30 years of age (44). In fact, while the limbic system undergoes remarkable remodeling during puberty, prefrontal areas development is not complete until near the age of 25 (45). In this study, though 96% of the participants in this study were over 18 years old, the number of people aged 18–25 accounts for nearly 80% of the total population. According to the neurobiological model of addiction, neurodevelopmental changes occurring during young people lead to an imbalance between emotional (reward motivation) and executive control (46, 47). This neurobiological fragility may contribute in young people to a higher risk of developing addictive behaviors (48).

This study also found that in the online game group, the proportion of males was significantly higher than that of females ($P < 0.001$), which is consistent with previous research (49, 50). The differences in user needs between males and females could be the possible reason. Researchers have indicated that males prefer to get novel, stimulating, and exciting game experiences through online games, while females tend to maintain a real relationship through online social chat (51).

According to the standards of the original scale, those with scores of 30 and above are considered to be IGA subjects. However, there were no subjects with scores of 30 and above in this study. The reason for this might be that the subjects selected focus only on college students. Well-educated college students have better self-management abilities and hence lower rates of addiction. Some studies have found that even among the general population, only 0.3–1.0% of people meet the diagnostic criteria of IGA (11). On the other hand, the sample size of this study was not adequately large.

LIMITATION

We investigated college students in Northern Anhui, China, the sample size of this study was not adequately large and the research subjects were only college students. Therefore, the results of this study need to be verified with a larger sample size and an expanded scope of research. This study only used questionnaire survey, and the results might be partially subject to subjectivity. Further research that includes brain imaging and neurophysiology is also necessary to corroborate the results of this study.

CONCLUSIONS

This study identified a dual role of online games. Moderate online game activities could improve the emotional state and executive function of college students. However, excessive online game behavior that does not reach the degree of addiction can also negatively affect emotional state and executive function. The imbalance between reward motivation and executive control might contribute to IGA. This study suggests that online game activities should not be completely denied, but the emotional state and executive function of those who indulge in online games should be monitored. Pre-intervention can prevent game behavior turning into an addiction.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Bengbu Medical College. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

WZ and TW wrote the first draft of the manuscript. DJ and RZ provided critical revision of the manuscript for important intellectual content. All authors have materially participated in the manuscript preparation and gave input to the manuscript text and approved the final version of the manuscript.

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Developing an App to Screen for Dual Disorders: A Tool for Improving Treatment Services in Mexico

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Background: Previous studies in Mexico undertaken at residential facilities for treating substance use disorders (SUDs) reported that the prevalence of Dual Disorders (DDs) is over 65%. DDs pose a major challenge for the Mexican health system, particularly for community-based residential care facilities for SUDs, due to the shortage of certified professionals to diagnose and treat these patients. Moreover, the lack of standardized algorithms for screening for and evaluating DDs to refer patients to specialized services (whether private or public) hinders timely care, delaying the start of integrated treatment. The use of new technologies provides a strategic opportunity for the timely detection of DDs through the development of standardized digital applications for the timely detection of DDs.

Objective: To develop an app to screen for DDs, which will contribute to referral to specialized services in keeping with the level of severity of psychiatric and addictive symptomatology, and be suitable for use by community-based residential care facilities for SUDs.

Method: The research project was implemented in two stages. Stage 1 involved obtaining the psychometric properties of the Dual Diagnosis Screening Interview (DDSI). Stage 2 consisted of two steps to test the *Beta* version of the app and the quality of version 1.0.

Results: The DDS obtained sensitivity and specificity scores above 85%. The app and its algorithm to screen for and refer DDs proved to be efficient and easy to apply with satisfactory community acceptance.

Conclusion: The app promises to be a useful screening tool at residential addiction treatment centers.

Keywords: dual disorders, substance use disorders, treatment, screening, m-Health, ICTs

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BACKGROUND

Overview of Dual Disorders

Several clinical research studies have reported high prevalence of Dual Disorders (DDs) or Co-occurring Disorders (the clinical correlation between substance use disorders and other psychiatric disorders) (1–3). Patients with DDs have complex symptomatology that produces a synergistic effect between the two dimensions, increasing the

level of severity and negatively impacting those who suffer them (4). DDs are associated with a higher risk of sexually transmitted infections, suicidality (ideation, behavior and attempts), school and work dropout, legal problems, and greater biopsychosocial deterioration (5).

Despite the reports, there are barriers to accessing adequate treatment. The scientific literature has identified two broad categories to service access: personal characteristics and structural barriers. Personal characteristics include personal vulnerabilities associated with the symptomatology and severity of both psychopathological dimensions, in addition to the motivation to change and personal beliefs associated with preconceived ideas about health professionals, stigma and cultural differences (6). The review identified the following structural barriers: service availability, DD identification, service provision, racial and ethnic disparities and last but not least, insurance policies (6).

All treatment programs must offer standardized screening and assessment services to determine the locus of attention or level of care required by the needs and particularities of each patient (3).

Screening, Assessment, and Treatment Planning for People With DDs

Screening, assessment, and treatment planning constitute an interrelated process designed to explore, detect, inform, refer, diagnose, and plan the treatment of people with DDs in the best program available according to the needs of each patient. Understanding these three components (screening, assessment, and treatment planning) as an integrated process is key to successful treatment (7).

The screening component is a formal process that determines the likelihood that a patient with SUD will present signs, symptoms, or behaviors associated with other mental disorders or vice versa. Its purpose is not to establish a specific diagnosis, but to recognize the need for an in-depth assessment. The assessment component determines differential diagnoses and identifies other clinical characteristics such as readiness for change, strengths or problematic areas that may affect treatment and rehabilitation, and engages the patient in the treatment. Finally, the treatment planning component integrates treatment programs and interventions for both dimensions. The plan is tailored to the individual needs, readiness to change, preferences, and personal goals of the patient (7).

Despite evidence-based recommendations, not all programs have the same screening, assessment, and treatment services. Likewise, the range of competencies and expertise among health professionals varies enormously. Both aspects are obstacles to undertaking an integrative process. It is therefore essential to implement standardized procedures and tools to screen for and assess DDs according to the *locus* of care of each program (3).

Digital Tools for Screening Mental Disorders

The advantages of using screening tools include their ease of use and scoring, the limited training required for their administration, and, for well-researched tools, a known level of reliability and available cut-off scores. One disadvantage of screening instruments is that they sometimes become the only component of the screening process. A second disadvantage is that a routinely administered screening instrument provides little opportunity to establish a connection with the patient. It is important to encourage patients to accept a referral for assessment and treatment if needed (7).

The growth of information and communication technologies in the past decade has spawned a revolution in the detection, assessment and treatment procedures of various medical specialties by promoting the development of multiplatform telehealth (telemedicine) methodologies and tools (e-health), as well as mobile health (m-health) featuring the use of mobile devices (such as smartphones, tablets, laptops and monitoring devices) due to their ease of access, portability, functionality and usability (8, 9).

In the field of mental health, apps have been developed for a range of purposes. Some offer self-directed treatment services and live video conferences for psychoeducation for patients and families, psychiatric and/or psychological treatment (counseling or psychotherapy) in individual or group modalities and self-help groups (10). There are also apps designed to screen for and/or evaluate mental health problems and addictions. These applications can be incorporated into standardized self-report instruments (scales and questionnaires) and/or used with the help of a health professional (structured or semi-structured interviews) (8, 11).

Screening apps generally use standardized instruments to screen for and monitor psychiatric symptoms (such as depression, anxiety, mania, psychosis, impulsivity and self-harm) and substance use (including aspects such as frequency, quantity, severity and craving) (12–15).

There is evidence, however, that self-report/self-monitoring apps for screening are inaccurate in that they fail to provide cut-off points, or use non-standardized instruments. (14, 16). Likewise, they may offer inappropriate recommendations for the real needs of users (potential patients), by over- or under-estimating the actual state of health of the user (10). Moreover, it has been reported that about half the applications found in stores (App Store and Google Play) make claims about their effectiveness, although the evidence they present is based mainly on bibliographic searches with little methodological rigor or on personal involvement in their development (14).

Despite significant progress, the range of apps for DD screening is limited. To our knowledge, the only app for this purpose is the DDSI (Dual Diagnosis Screening Interview). This application is a practical tool for clinicians and based on a structured interview to screen for the following disorders: generalized anxiety, panic attack, agoraphobia, social phobia, specific phobias, posttraumatic stress disorder (PTSD), major depression, persistent depression (dysthymia), mania, psychosis, and attention deficit/hyperactivity disorder (ADHD) (17), but 2 years ago it stopped being available to download from commercial stores.

Dual Disorders in Mexico

The Mexican public network for the treatment of SUDs and their attendant problems comprises over 400 outpatient and 30

hospitalization units (2). However, as in other Latin American countries, state capacity for dealing with health problems is limited (18), particularly in patients with high levels of symptom severity.

For this reason, in Mexico, about a third of those with SUDs receive treatment at community-based residential care facilities for SUDs. These facilities (totaling over 2,000) are a popular alternative for recovery from addictions since many of them are designed to meet service demand quickly, particularly among patients in a state of substance intoxication with agitated or disruptive behavior. They are located in marginal areas, which makes them more affordable. Their services are much cheaper than private professional services, which most of those affected are unable to afford. They are usually based on the 12-step model of Alcoholics Anonymous (peer-to-peer care), offering treatment of varying lengths ranging from 3 to 12 months (19, 20).

Official reports indicate that about 91% of subjects receiving treatment in these settings are men aged between 18 and 30. Five per cent have used injection drugs, 64% report having shared needles despite being aware of the health risks and at least 2% are living with HIV (21). Other studies have found that about 75% of individuals have shown a lifetime prevalence of DDs (22), while over 60% have done so in the past 30 days (2).

However, despite their strengths, the majority of these community centers face significant constraints due to their limited physical and technological infrastructure, insufficient funds, untrained staff, and lack of standardized screening, assessment and treatment planning procedures and mental health professionals (19, 20).

The scientific literature has widely documented the potential problems faced by non-specialized health personnel when evaluating and treating people with mental health problems and addictions, especially when they lack training and supervision (23–25). In this respect, we inferred that the peer-to-peer care model with untrained staff and a lack of standardized procedures for treating patients with DDs increases the risk of iatrogenic harm, malpractice and negligence (26–28).

Nonetheless, despite their structural limitations and lack of specialized personnel, community-based residential care facilities for SUDs are in high demand for those with DDs. As a result, the Mexican government has made great efforts to regulate services by establishing minimum operating standards (29), and to certify the skills of paraprofessional staff (peers) (30). According to the evidence, it is essential to implement screening services as part of a standardized admissions process. The foregoing is intended to prevent, as far as possible, the presence of malpractice and negligence, and to reduce the risk of iatrogenic harm due to the lack of skills of paraprofessional staff (peers) and the shortage of qualified health personnel to assess and treat patients with DDs.

The aim of this study is to develop an app to screen for DDs that will improve the services offered by community-based residential care facilities for SUDs in Mexico, using an algorithm to detect the degree of severity of psychiatric and addictive symptomatology, and to contribute to the detection, counseling and referral of patients to specialized services.

METHODS

The research project was implemented in two stages. The purpose of Stage 1 was to obtain the psychometric properties of the Dual Diagnosis Screening Interview (DDSI), and to determine its validity by comparing it to a gold standard such as the Mini International Neuropsychiatric Interview (MINI). Stage 2 consisted of two steps to test the *Beta* version of the app and the quality of version 1.0.

All the study procedures, informed consent, evaluation forms and recruitment materials used were approved by the Ethics and Research Committee of the Ramón de la Fuente Muñiz National Institute of Psychiatry (INPRFM) (No. IC17055.0) and adhered to the recommendations of the World Medical Association, and the Declaration of Helsinki on international good practices for research in human beings.

Stage 1

Design, Sites, and Participants

A cross-sectional study with a convenience sample was implemented at 33 community-based residential SUD treatment facilities in Mexico City. Eligible participants met the following criteria: men and women aged $\geq$18 years, who had spent at least seven days in residential treatment to control for the residual effects of recent intoxication, who were literate and had signed the informed consent form. Participants with disabling symptoms of psychosis, mania (MINI) (31) and cognitive impairment (MoCA) (32) were excluded. Data were collected between February and December 2017.

Measures

Sociodemographic Data and Substance Use

This questionnaire is based on the Addiction Severity Index (33), following the recommendations of Mäkelä (34). The sections included sociodemographic data (age, sex, education, marital status, and source of economic income), substance use (impact substance, age of onset, years of use, use in the past 30 days, route of administration, and days of abstinence) and health service use (type of health service, health issue, and professional help).

Mini International Neuropsychiatric Interview (MINI)

This structured interview is used for the rapid, accurate diagnosis of psychiatric disorders according to DSM-IV criteria (31). An adapted, Spanish-language version was used. For this study, the following lifetime diagnoses from the MINI version were used in the analyses: mania/hypomania episode, psychotic disorder, depressive disorder (major episode or dysthymia), suicide attempt, alcohol use disorder, drug use disorder, PTSD, anxiety disorders (panic disorder, general anxiety disorder, specific or social phobia), antisocial personality disorder, and adult ADHD.

Dual Diagnosis Screening Interview (DDSI)

This brief interview evaluates the most frequent and severe psychiatric disorders found in substance users: depression, dysthymia, mania, psychosis, panic disorder, agoraphobia, simple phobia, social phobia, generalized anxiety disorder, PTSD, and ADHD, and lasts 13–20 min. The DDSI has shown a sensitivity of $>$80%, and a specificity of $>$82% for the identification of lifetime

disorders such as depression, mania, psychosis, social phobia and specific phobia (17).

Procedures

Site Selection

The 33 selected facilities all complied with current Mexican regulations for addiction treatment (NOM-028-SSA2-2009), were willing to facilitate the study procedures, and were equipped with adequate facilities to ensure patient privacy during study assessments.

Field Team, Training, and Certification

The field team comprised psychologists, six interviewers with undergraduate studies, and two supervisors with graduate studies in clinical psychology. All members of the clinical team had been trained and certified in the procedures and evaluation of the study. Training consisted of a centralized five-day program, comprising theoretical and practical seminars. Certification was undertaken through a role-play exercise. Training and certification were provided by the research team.

Recruitment and Enrollment of Participants

Potential participants were recruited through a group discussion in which they were informed of the characteristics of the study. Interested participants underwent an individual informed consent and signing process, with an interviewer providing detailed information on the study, its risks and benefits, and subjects' rights. If they agreed to participate, subjects proceeded to sign the informed consent form and the interview began to be administered (MINI and DDSI), which took ∼2 hours. The interval between the administration of both instruments ranged from 3 to 5 days.

Statistical Analysis

The groups with and without DD were formed based on the presence of a psychiatric disorder identified by the DDSI. Univariate analyses were performed for demographic variables (sex, age, education, marital status) and substance use (in the past 30 days), chi-square (χ^2) for categorical variables and Student's t for numerical variables. DDSI efficiency (sensitivity, specificity, positive and negative predictive values) of the predictive variable in relation to the MINI was calculated and tested for statistical significance using a 2 × 2 Chi-Square test. Since missing data were assumed to be completely random (MCAR), we used multiple imputation for the missing data with the R statistical package. A significant value of $p < 0.05$ was used. All statistical analyses were performed using SPSS v23.

Stage 2

Stage 2, comprising two steps, was implemented between January 2018 and December 2019, to test and improve the components of the *Beta* version and test the quality of the 1.0 version of the app.

Step 1

After the psychometric properties of the DDSI had been obtained, the *Beta* version of the App was developed, which comprised basic functions and components such as patient file control, personal data, and substance use pattern forms, DDSI, and results reports.

To test the functionality and usability of the *Beta* version, the field team administered just over 60 interviews to identify possible errors and improvements. SCRUM (35) methodology was used to improve the interaction between the teams [field, research and Information and Communication Technologies (ICT)]. Accordingly, the necessary minimum was documented through user stories, and user acceptance tests (UAT) were much more dynamic, with rapid feedback for error correction.

To identify possible improvements to the procedures and components of the *Beta* version, working meetings were held between teams (field, research, and ICT). Results were collected at the end of the *Beta* version test, and it was deemed fit to generate usability reports and errors. Taking this as process input, activities were classified as error debugging, usability improvement, and component modification or the addition of new components.

Through the usability testimonials of the field, research, and ICT teams, needs for improvement were grouped into four categories: ability to adapt (enables the user to understand whether the software is suitable for their needs); learning capacity (enables the user to learn how to use it quickly and intuitively). Ability to be used (enables the user to operate and control the software with ease), and aesthetics of the user interface (is pleasing and satisfies the user's interaction with the application and visual elements are easy to locate).

Likewise, during the collaborative working sessions, the need to modify certain features and incorporate new ones was detected. To this end, clinical experts outside the project were consulted to validate and strengthen improvements. Modifications and additions of components were made according to the constraints of the project (time, personnel, and funds).

Step 2

To test the quality of version 1.0 of the app., the Mobile App Rating Scale (MARS) (36) was used in a group of 63 addiction and mental health professionals. This scale uses the mean scores of the engagement, functionality, aesthetics, information and subjectivity subscales, and MARS is scored according to the overall mean app quality score. MARS's psychometric properties have shown excellent internal consistency (Cronbach alpha = 0.90) with the total score and internal consistencies of the subscales also being very high (Cronbach alpha = 0.80–0.89, median 0.85) (36).

To achieve this goal, 100 addiction and mental health professionals from a state treatment agency were invited to participate by email. The invitation explained the dynamics of participation, which involved (1) participating in a video conference (ZOOM system) to explain the app and its usefulness. (2) Additionally, participants with Android devices were invited to participate in a demonstration of the installation and use of the app. (3) Android device users received an email with a file to install the app (*pd-s_v1.apk*), an installation video and a link to participate in the MARS online survey (using the SurveyMonkey system). The email also stated that participation was voluntary and anonymous, and that informed consent would be requested.

TABLE 1 | Participants' characteristics ($n = 213$).

	With dual disorder $n = 149$	Without dual disorder $n = 64$	Total $n = 213$	*Statistical differences*	*p*
	$\tilde{x}(sd)/n(\%)$	$\tilde{x}(sd)/n(\%)$	$\tilde{x}(sd)/n(\%)$		
Age	30.20 (10.99)	33.15 (11.21)	*31.09 (11.12)*	$t_{(211)} = 4.43$*	***0.007***
Sex				$\chi^2_{(1)} = 2.42$	*0.146*
Men	139 (93.3)	63 (98.4)	202 (94.8)		
Women	10 (6.7)	1 (1.6)	11 (5.2)		
Educational attainment				$\chi^2_{(3)} = 7.63$	*0.070*
None	0 (0)	3 (4.7)	3 (1.4)		
Elementary school	15 (10.1)	7 (10.9)	22 (10.3)		
High school	119 (79.9)	46 (71.9)	165 (77.5)		
College	15 (10.1)	8 (12.5)	23 (10.8)		
Marital status				$\chi^2_{(2)} = 6.81$*	***0.026***
Single	79 (53.4)	22 (34.4)	101 (47.6)		
Married/living together	34 (23.0)	23 (35.9)	57 (26.9)		
Widowed/Divorced/Separated	35 (23.6)	19 (29.7)	54 (25.5)		
Main source of economic income				$\chi^2_{(4)} = 4.16$	*0.112*
Employment	65 (43.6)	35 (54.7)	100 (46.9)		
Self-employment	5 (3.4)	3 (4.7)	8 (3.8)		
Family support	58 (38.9)	19 (29.7)	77 (36.2)		
Other	19 (12.8)	5 (7.8)	24 (11.3)		
None	2 (1.3)	2 (3.1)	4 (1.9)		
Impact substance				$\chi^2_{(4)} = 9.22$*	***0.033***
Alcohol	51 (34.2)	24 (37.5)	75 (35.2)		
Cocaine	48 (32.2)	22 (34.5)	70 (32.9)		
Marijuana	17 (11.4)	11 (17.2)	28 (13.1)		
Inhalants	27 (18.1)	6 (9.4)	33 (15.5)		
Other	6 (4.0)	1 (1.6)	7 (3.3)		
Use in past 30 days					
Alcohol	13.29 (11.7)	10.13 (10.37)	12.36 (11.39)	$t_{(198)} = 1.79$	*0.070*
Cocaine	11.17 (12.25)	10. 07 (12.61)	10.87 (12.32)	$t_{(165)} = 0.51$	*0.435*
Marijuana	13.41 (13.75)	9.74 (12.66)	12.42 (13.53)	$t_{(158)} = 0.15$	*0.732*
Inhalants	9.06 (12.15)	7.66 (11.88)	8.77 (12.06)	$t_{(113)} = 0.50$	*0.360*
Other	5.27 (10.01)	7.66 (12.15)	5.74 (10.42)	$t_{(90)} = -0.87$	*0.404*

*$p < 0.05$. *Bold indicates statistically significant values.*

RESULTS

Stage 1

A total of 213 participants (94.8 % male), with an average age of 31.09 ($sd = 11.12$) years, the majority of whom had completed junior and senior high school (87.8%), and nearly half of whom (47.6%) were single, (see **Table 1**) were selected. The group with DDs reported a lower age (30.20 years), had completed junior or senior high school (90%) and were mostly single (53.4%) in comparison with the group without dual disorders. In both groups, the main source of income was subordinate work followed by independent work, with the only statistically significant difference found between the groups being marital status ($\chi^2_{(2)} = 6.81$, $p = 0.026$). As for substance use, the substance with the greatest impact on participants with DDs was alcohol (34.2%), followed by cocaine (32.2%) and inhalants (18.1%), whereas in the group without DDs, the substance with the greatest impact was alcohol (37.5%), followed by cocaine (34.5%). No statistically significant differences were found between the two groups for use in the past month (see **Table 1**).

Psychometric Properties of DDSI

According to the results, the most prevalent diagnoses were depression (35.2%), PTSD (22.5%) and ADHD (21.1%). Additionally, the psychometric properties yielded sensitivity scores ranging from 0.81 for PTSD and psychosis to 0.88 for GAD, mania, and social phobia. Specificity scores were 0.85 or higher for most of the disorders screened. Finally, negative predictive values were <0.93 whereas positive predictive values were <0.54 for most of the disorders screened (see **Table 2**).

Stage 2

Step 1

The working meetings between the field, research and IT teams resulted in a backlog report. This report contains a record of all the errors (bugs) and navigation issues detected, together with

TABLE 2 | Psychometrics properties of DDSI ($n = 213$).

	Sensitivity	Specificity	PPV	NPV	TN	FN	TP	FP	Prevalence %
Depression	0.84 (0.75–0.92)	0.77 (0.69–0.84)	0.66 (0.56–0.76)	0.89 (0.83–0.95)	121	17	63	12	35.2
GAD	0.88 (0.74–0.91)	0.85 (0.79–0.90)	0.45 (0.30–0.59)	0.98 (0.95–0.98)	159	28	23	3	12.3
PTSD	0.81 (0.69–0.93)	0.75 (0.68–0.82)	0.48 (0.37–0.60)	0.93 (0.88–0.97)	124	41	39	9	22.5
Social Phobia	0.88 (0.69–0.94)	0.85 (0.80–0.90)	0.34 (0.19–0.50)	0.98 (0.96–0.99)	168	28	15	2	7.9
ADHD	0.86 (0.75–0.97)	0.89 (0.83–0.93)	0.67 (0.54–0.80)	0.96 (0.92–0.99)	149	19	39	6	21.1
PDD	0.87 (0.68–0.91)	0.92 (0.87–0.95)	0.46 (0.27–0.66)	0.98 (0.97–0.99)	181	16	14	2	7.6
Psychosis	0.81 (0.67–0.95)	0.86 (0.80–0.91)	0.54 (0.40–0.68)	0.95 (0.92–0.99)	151	25	30	7	17.3
Mania	0.88 (0.62–0.93)	0.93 (0.89–0.97)	0.38 (0.15–0.61)	0.99 (0.98–0.99)	189	13	8	1	4.2

GAD, Generalized anxiety disorder; PTSD, Posttraumatic stress disorder; ADHD, Attention Deficit / Hyperactivity Disorder; PDD, Persistent depression disorder; PPV„ Positive predictive value; NPV: Negative predictive value; TN, True negative; FN, False negative; TP, True positive; FP, False positive.

the need to modify existing components or incorporate new ones, which was prioritized by the field and research team.

Some of these errors (bugs) were redundant functions, elaborate code, and runtime errors. As for usability improvement, the backlog report documented certain navigation issues between screens or regarding the arrangement of elements and the inconsistent look and feel of components, and the need to modify them or incorporate new ones (see **Table 3**). As a result of all the improvements implemented, the 1.0 version was created, with better performance in intuitive/ergonomic navigation (see **Figure 1**) than the *Beta* version.

The most important component of the app is the traffic light algorithm designed to contribute to the rapid identification of probable psychiatric and substance use disorders, while providing the user with recommendations for assessment and referral to specialized treatment.

The algorithm assumes that screening is being carried out at a community residential treatment center where there are no specialized mental health professionals equipped to assess and treat patients with probable mental disorders other than SUDs.

Accordingly, the purpose of the algorithm is to identify possible mental disorders and prioritize assessment and treatment needs, distinguishing between conditions that constitute a genuine psychiatric emergency (psychosis, mania and suicide) from those that do not (see **Figure 2**) (39).

The algorithm generates three types of recommendations, based on a traffic light system:

Red Light

"The patient has probable psychiatric disorders co-occurring with substance use. This condition poses a **medium to high risk**. The recommendation is to refer the patient as a priority to a specialized institution for assessment and treatment".

Yellow Light

"The patient has probable psychiatric disorders co-occurring with substance use. This condition represents a **low to medium risk**. The recommendation is to refer the patient to a mental health specialist for assessment and treatment".

Green Light

"The patient does not have probable mental disorders co-occurring with substance use. This condition **does not represent an apparent risk**. The recommendation is to continue with standard treatment".

Step 2

A total of 100 addiction and mental health professionals were invited to participate, 85 of which agreed to participate in the videoconference and only 63 of which answered the survey. The average age of the health professionals was 39.71 years, most of whom were women. A total of 50.8% were doctors, 39.7% were psychologists and 9.5% were from other professions. Seventy-three per cent reported having completed postgraduate studies. Regarding the number of years of experience in mental health treatment, it was observed that the majority had over 6 years' experience (63.4%). Likewise, according to the MARS results, the app obtained a total quality score of 4.3. Moreover, it was observed that subjects with postgraduate studies, doctors, and those with fewer than 10 years' experience in mental health rated the app slightly lower (see **Table 4**).

DISCUSSION

The objective of the present study was to develop an algorithm to screen for DDs, which helps detect SUDs, counsel patients and refer them to specialized services according to the level of severity of their psychiatric and addictive symptomatology, through the use of an app that will be easy to use and adopt in Community-Based Residential Care Facilities for SUDs. To this end, the specificity of the DDSI was obtained as well as its concurrent validity against the gold standard (MINI). Likewise, a *Beta* version of the App was tested, which improved version 1.0 in terms of functionality, usability, and aesthetics. It also permitted the incorporation of components to increase the detection and measurement of other psychopathological aspects, as well as making clinical decision-making more efficient by incorporating the traffic light algorithm. Finally, the MARS scale was used to enable the quality of the app to be evaluated by mental health and addiction professionals, who evaluated it positively in the five dimensions (commitment, functionality, aesthetics, information, and subjectivity).

The results obtained during Stage 1 indicate that the sensitivity and specificity scores of the DDSI were similar to those of the original study (17), where they are above 80%. Conversely,

TABLE 3 | Component improvements.

Modification of components between versions	
***Beta* version**	**1.0 version**
Patient file control	**Patient file control**
- Record registration	- Record registration - Edit registration - Delete registration - View results report - Export Data base
Personal data	**Personal data**
- Sociodemographic data - Service use	- Sociodemographic data - Personal medical history - Personal psychopathology history - History of previous treatments
Substance use pattern	**Substance use pattern**
- Age of onset - Lifetime use - Use in past 30 days - Longer abstinence time - Administration route	- Age of onset - Lifetime use - Use in past 30 days - Longer abstinence time - Administration route
Screening instruments	**Screening instruments**
- Dual Disorder Screening	- Dual Disorder Screening* - Suicide Screening** - Alcohol Use Disorder Screening*** - Substance Use Disorder Screening****
Results report	**Results report**
- Visualization on mobile device	- Visualization on mobile device - Generation of results report in PDF file - Includes: Personal data, Substance use pattern, results of screenings, algorithm of recommendations, disclaimer, notes of evaluator and list of public institutions for assessment and treatment.

New component in 1.0 version

- **Algorithm of recommendations:** Offers patients recommendations for assessment and referral to specialized treatment.
- **User's manual:** The manual provides information on the requirements of the System, installation, navigation between screens, application interactions of the algorithm and data dictionary.
- **Terms of use**: These provide information on the disclaimer.
- **About:** This provides information on the research and development teams, institutions, funding, and endorsements.
- **Data base export:** This allows the export in CSV format of the database of evaluated patients stored in the device. The database includes all the variables of the forms administered.

*Dual Diagnosis Screening Interview (DDSI) *(17); Suicide **(31); Short Alcohol Dependence Data Questionnaire (SADD) ***(37); Drug Abuse Screening Test (DAST) **** (38).*

negative predictive values were higher over 90%, whereas positive predictive values ranged from 34 to 67%, These scores may be due to the fact that positive predictive values depend largely on the prevalence of a set condition (and to a lesser effect on specificity and sensitivity) as has been reported in various studies where low VPP have been obtained (40, 41). For this reason, it is estimated that when case prevalence increases, false positives fall, which makes VPPs increase. Future studies should be conducted on specific populations to determine whether VPPs increase with case numbers and do not depend on DDSI properties (42), although it may also be due to the symptoms of the addiction itself masking co-occurring psychiatric symptomatology (42). However, the DDSI can be said to be a valid, reliable screening tool suitable for use in clinical settings for the detection of possible mental disorders in people with substance use.

Additionally, results tally with those obtained in previous studies conducted in Mexico and Spain in residential and outpatient treatment centers. These data underline the fact that DD patients are the rule rather than the exception, with a prevalence of over 60% in the past 30 days. Most of them are polydrug users, with depression, anxiety, PTSD, psychotic disorders and ADHD being the most prevalent disorders (2, 17, 43, 44).

The procedure followed during step 1 resulted in version 1.0 of the App, which is significantly better than the *Beta* version, in that it eliminated recurring errors (bugs), allowing greater functionality and usability. It significantly improved the aesthetics of the interface and navigation between screens, making it more intuitive and cognitively ergonomic. In addition to the DDSI, key clinical scales (with validity, reliability, and cut-off points) were incorporated to screen for suicidality and

FIGURE 1 | App navigation flow chart. App Name: Patología Dual Screening. Description: It is an application for mobile devices to help health professionals in the timely detection of the co-occurrence between substance use disorders with other psychiatric disorders. Version: 1.0. Update date: January / 2020. Language: Spanish. Developed by: Unit of Clinical Trials in Addictions and Mental Health of the Ramón de la Fuente Muñiz National Institute of Psychiatry and the Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) / Barcelona. Cost: The application is free to use, it only requires requesting authorization from the corresponding institutions. Hardware / software requirements: 62Mb storage space. 50 Mb in RAM memory. Android operating system version 4.4 onwards. File size: 23Mb. PDF document reader.

drug and alcohol dependence (see **Table 3**). However, the most important feature is the inclusion of a traffic light algorithm that prioritizes the severity of the symptomatology assessed and provides recommendations according to the color of the traffic light (see **Figure 1**). Finally, this algorithm is linked to a detailed report of the screening process that facilitates feedback to the patient.

According to the results, it is extremely likely that the implementation of a screening service within community addiction centers in Mexico will allow non-specialized health personnel and para-professional counselors (peers) to identify, guide and, if necessary, refer patients for evaluation and treatment at a specialized public or private institution and thereby improve clinical decision-making for the benefit of patients, reducing the likelihood of negligence, malpractice and therefore iatrogenesis.

To ensure proper use of the app, institutions interested in implementing a screening service may request a 10-h in-person training package with three modules: (1) the theoretical framework of DDs, (2) basic aspects and use of the Dual Disorders Screening app and, (3) modeling and role play. This training will be available online shortly to facilitate access and achieve greater impact.

It should be noted that use of the Dual Disorders Screening app is not intended to replace professional psychiatric or psychological assessment, or the recommendations clinicians usually provide for patients. Accordingly, sensible, responsible use of the app is recommended, while communication with the treating psychiatrist should always be maintained.

Limitations

An obvious limitation is that the Dual Disorders Screening app was only developed for Android devices. However, it is important to mention that this decision was made because the Android operating system makes it possible to install programs unavailable at virtual stores such as Google Play, in addition to the fact that Android devices are significantly cheaper than those operating with iOS.

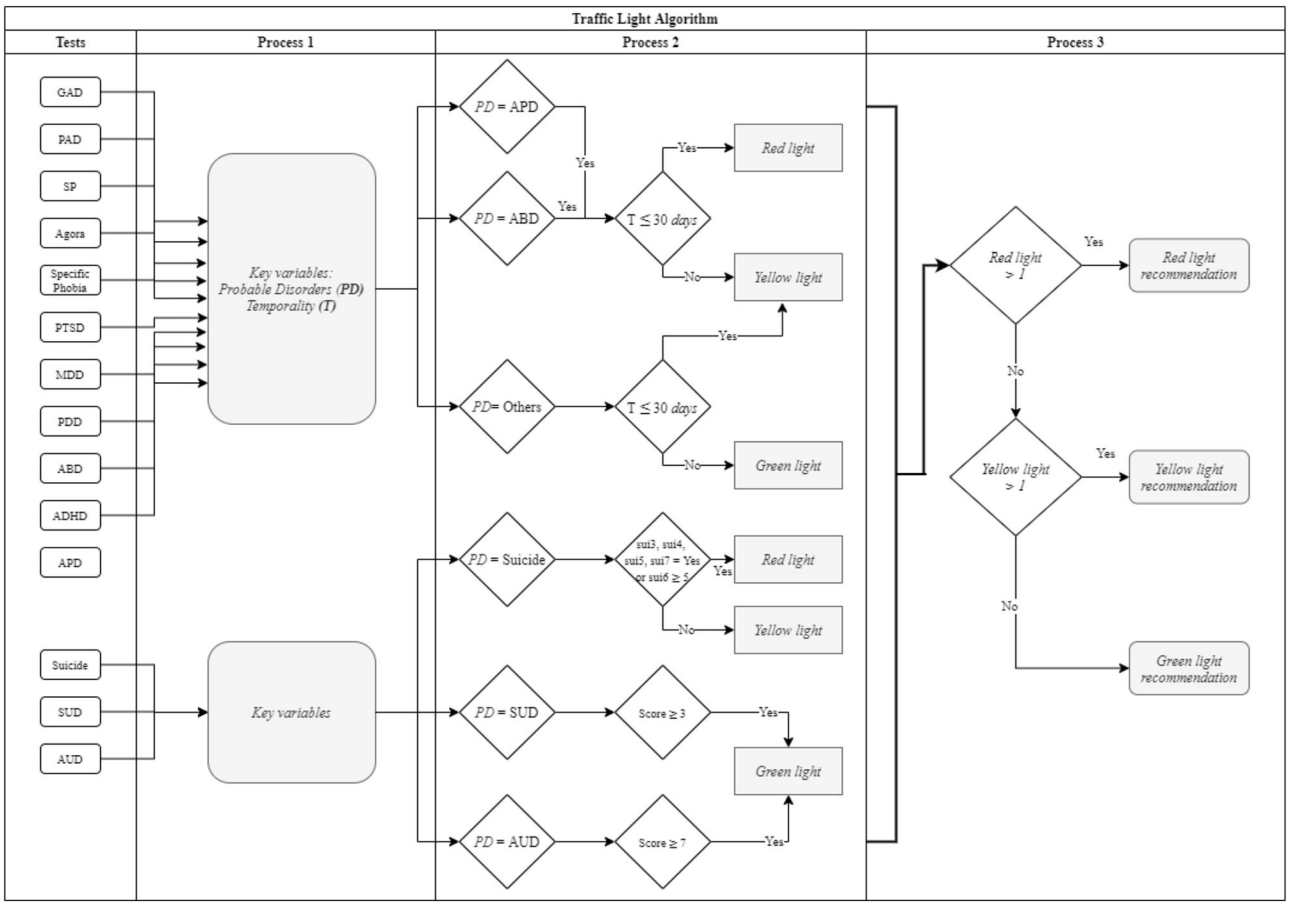

FIGURE 2 | Algorithm flow chart. Traffic Light Algorithm: IF probable APD, ABD, Suicide (ideation = true OR planning = true OR attempt = true OR intentionality ≥ 5) ≤ 30 days, THEN red light recommendation ELSE IF probable APD, ABD, Suicide (ideation = true OR planning = true OR attempt = true OR intentionality ≤ 4 OR lifetime attempt) > 30 days THEN yellow light recommendation, ELSE probable APD, ABD, Suicide = false AND Others > 30 days AND SUD ≥ 3 AND AUD ≥ 7 THEN green light recommendation.

TABLE 4 | Comparisons between MARS scores and demographic variables ($n = 63$).

	Engagement	Functionality	Aesthetics	Information	Subjectivity	Total
	$\tilde{x}(sd)$	$\tilde{x}(sd)$	$\tilde{x}(sd)$	$\tilde{x}(sd)$	$\tilde{x}(sd)$	$\tilde{x}(sd)$
Education						
Undergraduate	4.3 (0.78)	4.4 (0.59)	4.1 (0.75)	4.2 (0.61)	3.6 (0.69)	4.2 (0.63)
Graduate	4.1 (0.69)	4.2 (0.54)	4.1(6.9)	4.1 (0.76)	3.4 (0.67)	4.1 (0.59)
Profession						
Psychology	4.3 (0.63)	4.5 (0.36)	4.2 (0.57)	4.3 (0.59)	3.7 (0.68)	4.3 (0.46)
Medicine	3.9 (0.78)	4.1 (0.63)	3.9 (0.82)	3.9 (0.82)	3.3 (0.69)	3.9 (0.68)
Years of experience in mental health						
0–5 years	4.1 (0.79)	4.2 (0.65)	4.1 (0.81)	4.1 (0.81)	3.3 (0.73)	4.1 (0.70)
6–10 years	4.1 (0.73)	4.1 (0.54)	3.8 (0.68)	4.0 (0.73)	3.3 (0.62)	4.0 (0.61)
+ 10 years	4.2 (0.63)	4.5 (0.34)	4.2 (0.55)	4.3 (0.61)	3.7 (0.63)	4.3 (0.44)

Although the Dual Disorders Screening app is designed to be a practical tool to be used and adopted by community residential centers for addiction care in Mexico, it is understood that the app alone does not suffice. Accordingly, the development of a more robust electronic platform offering a broader range of services and products could serve as an extremely useful complement.

This platform should have e-health services such as electronic medical records compatible with RIS/PACS and LIS applications. It should also have telemedicine services for the distance training of community physicians and psychologists in the treatment of patients with DDs, as well as programs incorporating case supervision by psychiatrists and psychologists specializing in

DDs. Finally, there should be m-health-based support tools for patients and community professionals.

CONCLUSION

The Dual Disorders Screening app is a reliable tool for the detection of DDs, as well as the measurement of other clinical aspects associated with this population. It is hoped that the incorporation of the traffic light algorithm will enhance the clinical decision-making of personnel at community residential centers for addiction care throughout the country, thereby contributing to the improvement of public policy on addiction treatment in Mexico.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics and Research Committee of the Ramón de la Fuente Muñiz National Institute of Psychiatry (INPRFM) (No. IC17055.0). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM-N and MT were the principal investigators, they designed, developed and implemented of the research project, and conduct the manuscript. AT-F and JM-P were the implementation coordinators. RS-D and AP-L were supervisors during the field work and contribute for the statistical analysis. EM-DL, RS-A, and NS made significative contributions as an experts in Dual Disorders for the elaboration of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.697598/full#supplementary-material

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Descended Social Anxiety Disorder and Craving in Women Heroin Dependence Through Exercise Alerts Plasma Oxytocin Levels

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Purpose: This study explored the association between peripheral blood oxytocin (OT) and social anxiety disorder (SAD) and cue-induced cravings in female heroin addicts. The effect of exercise on alleviation of SAD and OT levels was also explored.

Methods: A total of 72 females with heroin dependence were assigned to three groups based on SAD severity. The three groups were Non-SAD control, SAD control, and SAD exercise groups. Subjects in the SAD exercise group underwent aerobic exercise and resistance training for 8 weeks (60 min/day, 5 days/week). Enzyme-linked immunosorbent assay analysis and Liebowitz Social Anxiety Scale (LSAS) scores were used to determine plasma OT concentration and SAD, respectively. Cue-induced craving was assessed using Visual Analog Scale (VAS) and Desires for Drug Questionnaire (DDQ). Mixed-effect analysis of variance and Pearson correlation analysis were used to explore the effect and correlation between different parameters.

Results: OT levels in the SAD exercise group were significantly high after exercise ($p < 0.01$). LSAS, VAS, and DDQ ("Desire and Intention" and "Negative reinforcement") scores in the SAD exercise group were significantly lower after exercise ($p < 0.01$). Plasma OT level was negatively correlated with LSAS score ($r = -0.534$, $p < 0.001$), VAS score ($r = -0.609$, $p < 0.001$), "Desire and Intention" score ($r = -0.555$, $p < 0.001$), and "Negative reinforcement" score ($r = -0.332$, $p < 0.01$) and positively correlated with the "control" score ($r = 0.258$, $p < 0.05$). LSAS was positively correlated with VAS score ($r = 0.588$, $p < 0.001$) and "Desire and Intention" score ($r = 0.282$, $p < 0.05$).

Conclusions: The findings of the present study indicate that plasma OT is a potential peripheral biomarker for prediction of the severity of social anxiety in female heroin withdrawal patients. Aerobic exercise combined with resistance training plus incremental load for 8 weeks can increase plasma OT levels and significantly reduce severity of SAD and cue-induced cravings in female heroin addicts.

Keywords: exercise, oxytocin, SAD, VAS, DDQ, craving

INTRODUCTION

Social anxiety disorder (SAD) is mainly caused by a combination of environmental and genetic factors. SAD is characterized by discomfort in various social contexts, such as public speaking, interaction with visitors, or dealing with strangers. Studies report higher incidence of SAD in women relative to men (1–3). People with severe SAD exhibit various physical reactions such as headaches, cold sweats, and gastrointestinal discomfort, which may lead to social avoidance (4). In addition, severe SAD can lead to substance use disorders (SUD) (5). A previous study reported that SAD affects the rate of relapse among drug addicts to some extent. Individuals with SAD have a high risk of developing SUD (6). The study reports that patients with SAD have a two-fold risk of using heroin compared with subjects without SAD (7). SAD is common among patients seeking SUD treatment. A previous study reported that a quarter of patients seeking opiate dependence treatment exhibited SAD (8). In addition, a study reported patients who received pharmacotherapy for opiate dependence had higher SAD levels compared with controls (9). Moreover, findings indicate that half of substance dependence patients have clinically elevated SAD (10). Studies indicate that heroin dependence is associated with social avoidance during withdrawal owing to the high level of physical dependence and emotional disorders (11).

OT is a neuropeptide that is released into the bloodstream from the posterior pituitary and it exhibits several central and peripheral blood effects (12). In addition, OT regulates several aspects of social cognition, social behaviors, and fear conditioning. These effects result in SAD and other disorders associated with impaired social functioning (13). OT levels are high in females relative to the level in males (14). Notably, OT protects females from SAD. Hoge reported low plasma OT levels in patients with a generalized SAD during a pro-social laboratory task paradigm (15). A study by Meyer-Lindenberg indicated that increased levels of OT may prevent SAD (16).

Moreover, OT plays a vital role in establishing clinical experimental models of addiction, relapse, and craving. Studies report that daily peripheral blood OT administration lowers self-administration of heroin in heroin-tolerant rats (17). In addition, OT can attenuate craving and alleviate withdrawal symptoms in female heroin-dependent patients; thus, it is a potential therapy for heroin dependence (18). Furthermore, OT decreases stress and cued reinstatement of opioid seeking (19). OT improves multiple aspects of social functioning, including emotion recognition (20) as well as social abilities in patients with opioid use disorder. These effects ultimately promotes engagement of the patients in psychosocial treatments and social support systems (21).

Regular aerobic exercise increases the plasma OT level in female mice, reduces anxiety, and increases emotions (22). Jazaieri reported that aerobic exercise can improve SAD (23). Effect of exercise on drug addiction and relapse process has been extensively studied and studies report that Qigong can prevent heroin detoxification without side effects (24). In addition, a significant association was observed between exercise and substance abuse in women compared with men (25). SAD and heroin dependence are correlated with OT levels.

The aim of the current study was to explore whether the degree of SAD in heroin withdrawal subjects was correlated with the level of peripheral blood OT. Moreover, the effect of exercise on peripheral blood OT levels, SAD levels, and cue-induced cravings in heroin withdrawal subjects was explored.

STUDY SUBJECTS AND METHODS

Subjects

A total of 72 subjects with opioid dependence (aged 35–50 years) attending the Female Detoxification Rehabilitation Center of Baimalong in Hunan province were enrolled in this study. Interviews were conducted following guidelines by Structured Clinical Interviews and Statistical Manual (The Diagnostic and Statistical Manual of Mental Disorders-V, DSM-V) to explore whether participants had SAD. Structured interviews were conducted by clinical psychologists. ADIS-IV-Lifetime (ADIS-IV-L) (26) is a structured interview guideline designed to assess current and past (lifetime) diagnoses of anxiety disorders. It allows differential diagnosis of anxiety disorders based on DSM-V criteria. Anxiety Disorders Interview Schedule Lifetime Version (ADIS-IV-L) manual is highly effective for principal diagnosis of SAD (27). Diagnosis of SAD and collection of severity data were carried out using the Liebowitz SAD Scale-self-reported (LSAS-SR) scale. Individuals without SAD were included after screening using the same procedure. SAD patients comprised patients with a score $\geq$60, whereas Non-SAD included individuals with a score $<$30 based on the LSAS-SR scale (28, 29).

Exclusion criteria were as follows: (1) history of neurological, psychiatric disease and diagnosis of other mental disorders, except SAD; (2) dependence on other substances; (3) participants diagnosed with bone, muscle, and cardiovascular diseases; (4) individuals with vision and hearing impairment; (5) participants who have taken β-blockers a week before the study; and (6) participants who had not been assessed using Physical Activity Readiness Questionnaire Plus (PAR-Q+).

This study was conducted in accordance with the Declaration of Helsinki. Approval to conduct the study was obtained from the Institutional Review Committee of Hunan Normal University. A total of 52 SAD patients were randomly assigned into two groups: 26 in the control group and 26 in the exercise group. Eight people withdrew from the study owing to force majeure reasons such as family reasons, blood draw failure, and voluntary abandonment. The withdrawal rate was 15.3%. Twenty-two out of the 44 participants who left after withdrawal were assigned into the SAD control group and 22 participants were assigned into the SAD exercise group. In addition, 1 out of the 20 Non-SAD participants withdrew with a withdrawal rate of 10%; thus, 19 participants were assigned into the Non-SAD control group. See **Figure 1** for the participant screening process flowchart. The demographic characteristics of heroin addicts are shown in **Table 1**.

Procedure

This study was conducted from December 2018 to May 2019. In December 2018, the corresponding author conceptualized the study and contacted the rehabilitation center. Data on basic information and drug use were obtained from female patients

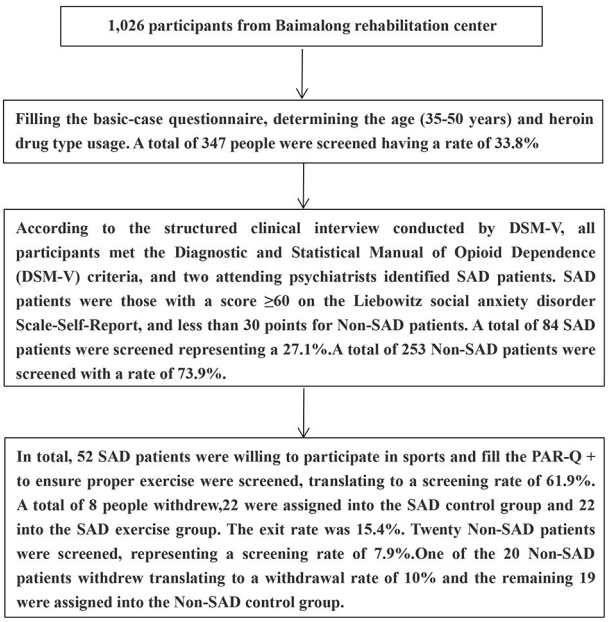

FIGURE 1 | A flowchart of the participant screening process.

attending the Baimalong Female Drug Rehabilitation Center in Hunan Province in January 2019. SAD diagnosis was performed on subjects who met the inclusion criteria, and data on drug use status and medical health conditions were obtained in February 2019. Clinical psychologists made judgments on patient status using structured interviews and SAD questionnaires. Pre-exercise screening and participation willingness surveys were conducted on selected subjects in February 2019 to ensure the suitable exercise is used and to confirm voluntary participation. The exercise intervention was conducted for 8 weeks. Preliminary blood collection, administration of SAD questionnaire, craving questionnaire survey, and exercise intervention were carried out in March 2019. Post-stage blood collection, administration of SAD questionnaire, craving questionnaire survey, and exercise intervention were carried out in May 2019.

Exercise Intervention

SAD exercise group received exercise intervention whereas subjects in the Non-SAD control and SAD control groups received safety and health education. Exercise intervention comprised aerobic combined resistance training according to ACSM guidelines (30). Each exercise session was conducted for a duration of 8 weeks (60 min/day, 5 days/week). The 60-min exercise program was conducted as follows: warm-up for 5 min, aerobic exercise on a treadmill or spinning exercise for 30 min, weight training for the main muscle groups (arms, chest, back, and legs) for 20 min, and stretching and relaxing for 5 min. A heart rate monitor (PolarTM RS400, Polar Inc, USA) was used to continuously monitor the heart rate throughout the training process. Monitoring of heart rate was conducted to ensure 30 min of continuous aerobic exercise in a predetermined heart rate zone. The treadmill rotation speed in the first 2 weeks was set at a target intensity of 40–60% heart rate reserve (HRR) (31). Subsequently, the treadmill speed was adjusted to a target intensity of 50–70% HRR in the third week. Intensity of weight training was 10–15RM. Four experienced physical exercise coaches directly supervised the training program.

Physical Activity Readiness Questionnaire Plus

PAR-Q+ is a four-page document comprising questions designed to identify possible restrictions or limitations for physical activity participation. Use of PAR-Q+ helps doctors and sports professionals to explore eligibility of participants before they undergo exercise training.

Liebowitz Social Anxiety Disorder Scale

LSAS (32) is a 24-item interviewer-rated instrument used for assessment of fear/anxiety and to prevent specific social situations. Respondents were required to rate their fear/anxiety (LSAS-Anxiety subscale) on a four-point scale ranging from 0 (none) to 3 (severe) (first column). Furthermore, participants rated their avoidance level (LSAS-Avoidance subscale) based on a four-point scale ranging from 0 (never) to 3 (usually) (second column). LSAS-SR (self-reported) was used in the present study as it is suitable for Chinese patients and has high reliability and validity. LSAS-SR has good sensitivity and specificity in diagnosis of SAD (33).

Craving Analysis

Desires for Drug Questionnaire

Self-evaluation of instant cravings among female subjects with heroin dependence was performed using DDQ. The questionnaire comprises three dimensions, namely, desire and intention (question numbers 1, 2, 4, 6, 9, 12, and 13), negative reinforcement (question numbers 5, 8, 10, and 11), and the control (question numbers 3 and 7).

Visual Analog Scale

VAS is used to visually assess immediate desire for heroin by patients. A 0- to 100-mm VAS scale was adopted for determining the degree of cue-induced craving (0 means "no craving," 100 means "extreme craving"). The patient was requested to relax for 5 min and then watch neutral pictures and videos for 5 min. Furthermore, the patient was requested to watch pictures and videos of objects, utensils, and heroin inhalation and play sound effects for 5 min. The heart rate and blood pressure were then determined immediately after cue induction was completed. VAS and DDQ were administered immediately after induction process. Psychological scale assessments and blood index testing were conducted a day before conducting the exercise intervention and a day after termination of exercise intervention.

Enzyme-Linked Immunosorbent Assay

Blood samples were collected from participants between 8:00 and 9:00 a.m. in the morning on the day before and the day after exercise intervention. Subjects who underwent blood sample collection starved from 8:00 p.m. the previous evening. Two milliliters of venous blood was collected into an EDTA

TABLE 1 | Demographic characteristics of heroin addicts.

Variable		Non-SAD control ($n = 19$)	SAD control ($n = 22$)	SAD exercise ($n = 22$)
Demographic and health characteristics				
Age (years)		40.26 ± 4.86	38.36 ± 5.69	39.55 ± 5.55
Height (cm)		160.21 ± 4.53	160.82 ± 4.69	159.32 ± 5.15
Weight (kg)		58.93 ± 6.11	59.93 ± 6.81	56.35 ± 5.15
BMI (kg/m^2)		27.71 ± 5.01	22.19 ± 1.60	23.21 ± 2.90
Waist (cm)		81.89 ± 6.70	82.50 ± 8.38	77.64 ± 4.35
Culture	Primary school or less	4 (21.1)	3 (13.6)	3 (13.6)
	Junior high school	7 (36.8)	9 (40.9)	13 (59.1)
	Senior middle school	5 (26.3)	5 (22.7)	6 (27.2)
	College or above	3 (15.8)	5 (22.7)	0 (0)
Occupation	Unemployed	2 (10.5)	10 (45.5)	15 (68.2)
	Self-employed	4 (21.1)	7 (31.8)	3 (13.6)
	Service	5 (26.3)	2 (9.1)	2 (9.1)
	Manual worker	4 (21.1)	1 (4.5)	1 (4.5)
	General staff	4 (21.1)	2 (9.1)	1 (4.5)
Marital status	Married	10 (52.6)	4 (18.2)	2 (9.1)
	Single	8 (42.1)	15 (68.2)	10 (45.5)
	Widowed	0 (0)	0 (0)	1 (4.5)
	Divorced	1 (5.3)	3 (13.6)	9 (40.9)
Regions	Urban	12 (63.2)	10 (45.5)	10 (45.5)
	Rural	7 (36.8)	12 (54.5)	12 (54.5)
Drug data				
Heroin use at one time (g)		0.52 ± 0.33	0.56 ± 0.33	0.45 ± 0.23
Times per month		20.46 ± 10.42	19.68 ± 11.52	21.25 ± 10.68
Duration (months)		116.41 ± 61.54	116.71 ± 64.35	12.34 ± 71.66
Relapse times		1.15 ± 0.57	1.58 ± 0.71	2.16 ± 1.17

anticoagulant test tube. The blood samples were mixed with anticoagulant before centrifugation at 4,000 rpm for 4 min. The supernatant was obtained and stored in an ultralow-temperature refrigerator at −80°C for further analysis. Blood indicators were analyzed at the Shanghai Enzyme Link Company.

Statistical Analysis

Mixed-effect analysis of variance was performed to explore the effect of group and time before and after exercise on the LSAS, VR-VAS, DDQ scores, and plasma OT levels in heroin-dependent females. Bonferroni method was used in the post-test for cases where $p < 0.05$ for pairwise comparisons between groups. Pearson correlation analysis was utilized to explore the relationship between plasma OT levels and LSAS, VAS, and DDQ scores of the three groups. All statistical analyses were conducted using SPSS 20.0 software. Data were expressed as mean ± standard deviation (M ± SD).

RESULTS

Results of LSAS, VR-VAS, and DDQ Pre-exercise and Post-exercise

Mixed-effect analysis of variance was conducted to explore the effects of groups and time on LSAS score. The results showed that group and time significantly affected LSAS score ($p < 0.001$), and a significant interaction was observed between group and time ($p < 0.001$). The LSAS score of the Non-SAD control group was lower relative to the LSAS scores of the SAD control (95% CI: −52.98, −43.72) and SAD exercise groups (95% CI: −54.12, −44.86) ($p < 0.001$) during the pre-exercise period. LSAS scores for the SAD control group and the SAD exercise group were not significantly different during the pre-exercise period ($p > 0.05$). LSAS score for the SAD exercise group was significantly lower compared with the LSAS score for the SAD control group ($p < 0.001$, 95% CI: −30.38, −17.90) during the post-exercise period. Notably, the LSAS score of the SAD exercise group was significantly lower after exercise compared with the LSAS score before the exercise ($p < 0.001$, 95% CI: 22.59, 30.86) (**Table 2**).

The effects of group and time on VAS were explored through mixed-effect analysis of variance. The results showed a significant effect of group and time on VAS ($p < 0.001$), and a significant interaction was observed between group and time ($p < 0.001$). VAS score of the Non-SAD control group was significantly lower relative to VAS score of SAD control group (95% CI: −26.74, −7.76) and the VAS score of the SAD exercise group during the pre-exercise period (95% CI: −22.93, −3.95) ($p < 0.001$). However, VAS scores of the SAD control group and the SAD exercise group were not significantly different ($p > 0.05$, 95% CI: −5.32, 12.96). The VAS score in the SAD exercise group was

TABLE 2 | The effect of exercise on LSAS score.

Group	Pre-exercise	Post-exercise	*p* (intergroup)	*p* (time)	*p* (interaction)
Non-SAD control	22.11 ± 2.87	21.58 ± 3.31	<0.001	<0.001	<0.001
SAD control	70.45 ± 7.44$^{\Delta\Delta}$	69.00 ± 7.00$^{\Delta\Delta}$			
SAD exercise	71.59 ± 6.41$^{\Delta\Delta}$	44.86 ± 12.02$^{\blacktriangle\blacktriangle,**}$			

$^{\Delta\Delta}p < 0.01$, *compared with the Non-SAD control group;* $^{\blacktriangle\blacktriangle}p < 0.01$, *compared with the SAD control group;* $^{**}p < 0.01$, *compared with pre-exercise.*

TABLE 3 | The effect of exercise on VAS.

Group	Pre-exercise	Post-exercise	*p* (intergroup)	*p* (time)	*p* (interaction)
Non-SAD control	24.47 ± 8.02	24.47 ± 9.31	<0.001	<0.001	<0.001
SAD control	41.72 ± 14.35$^{\Delta\Delta}$	39.55 ± 11.49$^{\Delta\Delta}$			
SAD exercise	37.91 ± 13.19 $^{\Delta\Delta}$	25.59 ± 9.36$^{\blacktriangle\blacktriangle,**}$			

$^{\Delta\Delta}p < 0.01$, *compared with the Non-SAD control group;* $^{\blacktriangle\blacktriangle}p < 0.01$, *compared with the SAD control group;* $^{**}p < 0.01$, *compared with pre-exercise.*

significantly lower compared with degree of craving for drugs in the SAD control group ($p < 0.001$, 95% CI: −21.65, −6.26) post-exercise. The VAS score of the SAD exercise group at 8 weeks was significantly lower compared with the VAS score before the exercise ($p < 0.001$, 95% CI: 7.93, 16.71) (**Table 3**).

The results showed no significant difference between the "Desire and Intention" and "Negative reinforcement" "Control" scores of the Non-SAD control group, the SAD control group, and the SAD exercise group before the exercise ($p > 0.05$). Subjects in the SAD exercise group showed significantly lower "Negative reinforcement" scores compared with the scores for the Non-SAD control subjects ($p < 0.01$, 95% CI: −1.66, −0.24) and the SAD control group after the exercise ($p < 0.05$, 95% CI: −1.49, −0.12). Scores for "Desire and Intention" (95% CI: 0.40, 1.23) and "Negative reinforcement" (95% CI: 0.35, 1.29) of the SAD exercise group after the exercise were significantly lower compared with the scores before the exercise ($p < 0.01$; **Table 4**).

Pre-exercise and Post-exercise Plasma OT Levels

The effects of group and time on plasma OT levels were explored through mixed-effect analysis of variance. The results showed that group significantly affected the level of plasma OT ($p < 0.001$); however, time point showed no significant effect on plasma OT level ($p > 0.05$). Notably, the findings showed a significant interaction between group and time ($p < 0.001$). The plasma OT level of the Non-SAD control group was higher relative to plasma OT levels of the SAD control group ($p < 0.01$, 95% CI: 1.54, 8.77) and the plasma OT levels of the SAD exercise group before the exercise ($p < 0.05$, 95% CI: 0.32, 7.55). However, the results showed no significant difference in the plasma OT level between the SAD control group and the SAD exercise group before the exercise ($p > 0.05$, 95% CI: −8.59, −3.02). However, the plasma OT level of the SAD exercise group was significantly higher compared with the plasma OT level of the SAD control group after the exercise ($p < 0.01$, 95% CI: 4.48, 12.72). The plasma OT level of the SAD control group was significantly lower relative to that of the Non-SAD control group after exercise ($p < 0.05$, 95% CI: −9.20, −0.24). The plasma OT level of the SAD exercise group showed significant increase after exercise compared with the pre-exercise plasma OT level ($p < 0.001$, 95% CI: −8.59, −3.02) (**Table 5**).

Correlation Analysis Results of Plasma OT Levels and LSAS, VAS, and DDQ Scores

Pearson correlation analysis was used to analyze the correlation between the plasma OT concentration and the LSAS, VAS, and DDQ scores. The results showed that the plasma OT concentration was negatively correlated with the LSAS score ($r = -0.534$, $p < 0.001$) and VAS score ($r = -0.609$, $p < 0.001$). Besides, plasma OT concentration was negatively correlated with both "Desire and Intention" score ($r = -0.555$, $p < 0.001$) and "Negative reinforcement" ($r = -0.332$, $p < 0.01$). Moreover, there was a positive correlation between the plasma OT concentration and the "Control" score ($r = 0.258$, $p < 0.05$; **Figure 2**).

Pearson correlation analysis was used to analyze the correlation between the LSAS score and the VAS, as well as the DDQ score. The results showed that the LSAS score was positively correlated with the VAS score ($r = 0.588$, $p < 0.001$) and "Desire and Intention"($r = 0.282$, $p < 0.05$). There was no correlation between the LSAS score and both "Negative reinforcement" ($r = 0.042$, $p = 0.742$), as well as "Control" score ($r = -0.219$, $p = 0.084$; **Figure 3**).

DISCUSSION

Participants under drug rehabilitation programs present with high number of drug-dependency complications compared with their counterparts. Previous studies report that SUD is significantly associated with SAD. Patients presenting with both SAD and SUD show severe complications compared with subjects with only a single disorder. Therefore, treatment of

TABLE 4 | The effect of exercise on DDQ.

Dimension	Group	Pre-exercise	Post-exercise	*p* (intergroup)	*p* (time)	*p* (interaction)
Desire and Intention	Non-SAD control	3.79 ± 0.92	3.95 ± 0.98	0.604	<0.05	<0.01
	SAD control	4.19 ± 1.24	4.07 ± 0.93			
	SAD exercise	4.34 ± 1.02	3.52 ± 0.91**			
Negative reinforcement	Non-SAD	4.39 ± 0.96	4.20 ± 1.10	0.063	<0.05	<0.05
	SAD control	4.21 ± 1.09	4.21 ± 0.91			
	SAD exercise	4.23 ± 0.93	3.41 ± 0.79$^{\Delta\Delta\blacktriangle**}$			
Control	Non-SAD control	3.63 ± 1.56	3.71 ± 1.18	0.228	0.276	0.958
	SAD control	2.97 ± 1.49	3.14 ± 1.26			
	SAD exercise	3.02 ± 1.29	3.16 ± 1.15			

$^{\Delta\Delta}p < 0.01$, *compared with the Non-SAD control group;* $^{\blacktriangle}p < 0.05$, *compared with the SAD control group;* $^{**}p < 0.01$, *compared with pre-exercise.*

TABLE 5 | The effect of exercise on plasma OT levels (pg/ml).

Group	Pre-exercise	Post-exercise	*p* (intergroup)	*p* (time)	*p* (interaction)
Non-SAD control	60.74 ± 3.91	58.93 ± 3.94	<0.001	0.332	<0.001
SAD control	55.58 ± 5.35$^{\Delta\Delta}$	54.01 ± 6.40$^{\Delta}$			
SAD exercise	56.80 ± 4.62$^{\Delta}$	62.61 ± 5.86$^{\blacktriangle\blacktriangle,**}$			

$^{\Delta}p < 0.05$, *compared with the Non-SAD control group;* $^{\Delta\Delta}p < 0.01$, *compared with the Non-SAD control group;* $^{\blacktriangle\blacktriangle}p < 0.01$, *compared with the SAD control group;* $^{**}p < 0.01$, *compared with pre-exercise.*

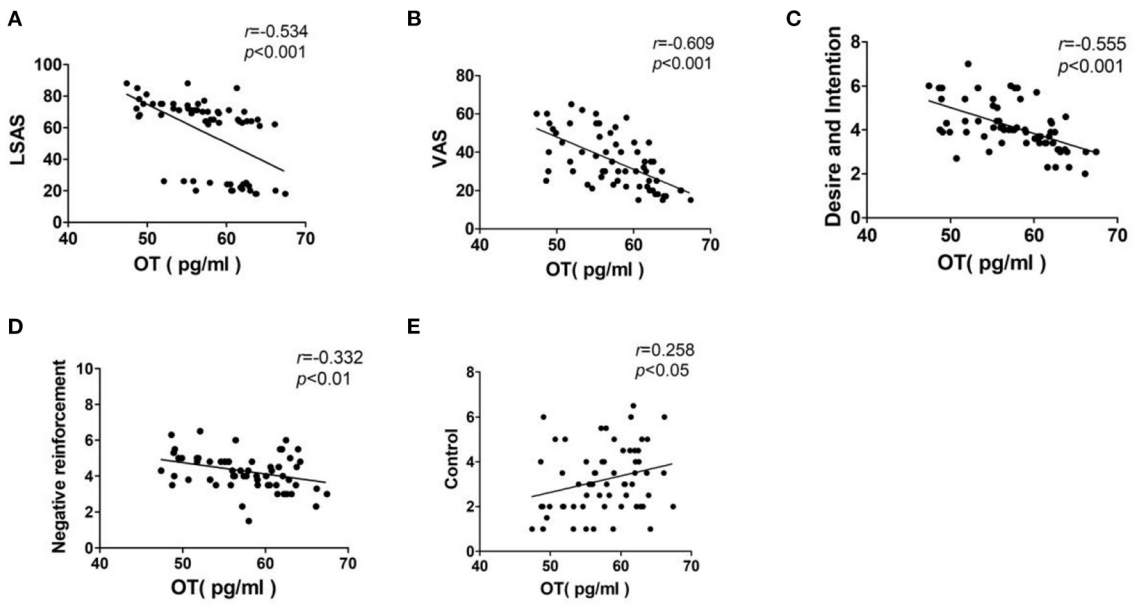

FIGURE 2 | Correlation analysis of plasma OT levels and the LSAS, VAS, and DDQ scores. Interpretation of *r*-value: 0 = no relationship; 0.01–0.19 = no/negligible relationship; 0.20–0.29 = weak positive correlation; 0.30–0.39 = moderate positive correlation; 0.40–0.69 = strong positive correlation; 0.70 or higher = very strong relationship. **(A)** LSAS, Liebowitz social anxiety disorder scale; **(B)** VAS, Visual Analog Scale; **(C)** Desire and Intention, desire for heroin; **(D)** Negative reinforcement, repeated use of heroin to relieve withdrawal symptoms; **(E)** Control, the ability to control heroin.

patients with SAD–AUD complications should not be limited to only a single disorder. Identification of possible similarities between the two treatments can provide a new therapeutic target for SAD–AUD patients. Correlation analysis based on LSAS, VAS, and DDQ scores shows a positive correlation between severity of SAD, VAS-craving, and "Desire and Intention," indicating an interactive relationship between SAD and AUD. However, the results of the present study showed no correlation

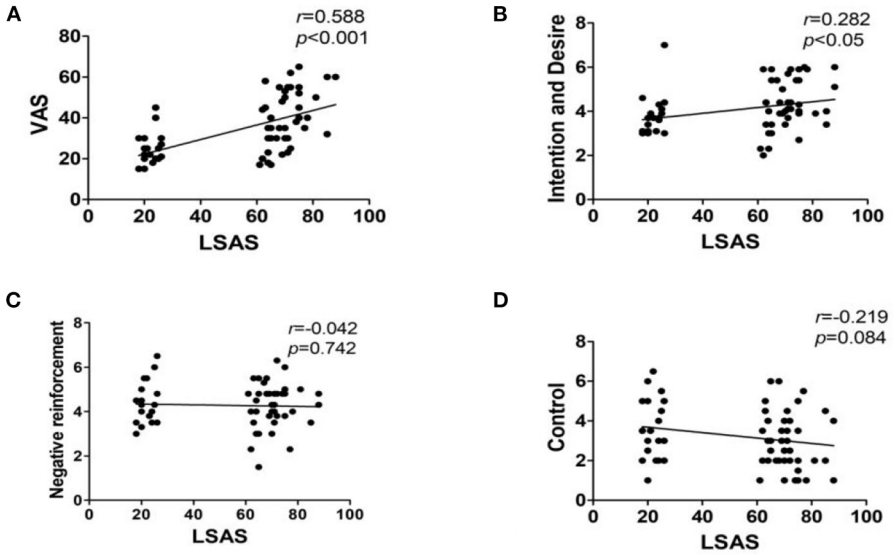

FIGURE 3 | Correlation analysis results of LSAS and the VAS, as well as DDQ scores. Interpretation of *r*-value: 0 = no relationship; 0.01–0.19 = no/negligible relationship; 0.20–0.29 = weak positive correlation; 0.30–0.39 = moderate positive correlation; 0.40–0.69 = strong positive correlation; 0.70 or higher = very strong relationship. **(A)** VAS, Visual Analog Scale; **(B)** Desire and Intention, desire for heroin; **(C)** Negative reinforcement, repeated use of heroin to relieve withdrawal symptoms; **(D)** Control, the ability to control heroin.

between "Negative reinforcement" and "Control" according to LSAS scores. This can be attributed to the small sample size used for the study or the high number of dropouts in this study. The findings showed significant differences in VAS-craving between the SAD group and the Non-SAD group. This implies that heroin addicts with SAD show high levels of fear during social interaction and social attachment. In addition, heroin addicts feel more inferior and nervous in social settings. Therefore, their inner loneliness increases, positive emotions decrease, and present with physiological arousal. These subjects thus rely on other ways to compensate for their inner positive emotions. Moreover, heroin addicts have the urge to compensate for their inner positive emotions when subjected to drug simulation cues. The pathological memory thus overlaps with physiological arousal and drug craving increases.

Studies report a positive association between OT and anxiety symptoms. For instance, a study comprising 29 patients with obsessive–compulsive disorder reported a higher OT level associated with more anxiety symptoms (34). Moreover, plasma OT level is positively correlated with anxiety composite scores in healthy women (35). On the contrary, Scantamburlo et al. (36) reported a negative correlation between anxiety symptoms and OT level in a group of 25 depressed patients. The findings of the present study exhibited a significantly high negative correlation between plasma OT levels and severity of SAD, which was consistent with the findings by Scantamburlo et al. (36). The severity of SAD and the baseline plasma OT levels were significantly different between SAD patients and Non-SAD patients. However, severity of SAD and the baseline plasma OT levels between the SAD control group and the SAD exercise group were not significantly different. This verified the correlation analysis results. Woolley et al. (21) conducted a study on the correlation between OT and heroin cue-induced cravings and reported that intranasal administration of a single OT dose to opioid users undergoing opioid replacement therapy was well-tolerated without significant effects on craving. This finding indicates a significant association between OT levels and heroin cues. Nikolaou et al. (37) reported a positive correlation between plasma OT levels of participants and scores based on COWS, VAS-Craving, and the Hamilton Anxiety scales. Contrary to these findings, Lin et al. (38) reported a negative correlation between plasma OT levels and craving levels in female heroin-dependent patients under methadone maintenance. The negative correlation was most significant in subjects with lower scores of novelty-seeking behaviors. VAS and DDQ scales were used in the present study to explore the relationship between cue-induced craving and plasma OT levels. The results showed that VAS-craving, "Desire and Intention," and "Negative reinforcement" scores exhibited a negative relationship with plasma OT levels. Notably, VAS assessment results showed significant correlation with OT levels compared with the relationship between "Desire and Intention" and OT levels. VAS has fewer dimensions and short time; thus, it is easy to directly reflect a relationship. Moreover, the finding indicates that the DDQ scale is used to complement VAS in determining the degree of desire. A consistent negative correlation using both DDQ scale and VAS scale indicates the relationship between plasma OT levels and cue-induced cravings.

The results showed that aerobic combined with resistance exercise for a period of 8 weeks increased plasma OT levels of heroin withdrawal and alleviated SAD and cue-induced cravings. The efficacy of AE can be explained by the fact that aerobic exercise mimics the same bodily sensations elicited by

anxiety reactions, such as increased heart rate, respiration, and perspiration (39). Therefore, exercise prompted the participants to differently evaluate their bodily responses (such as in a less threatening manner) compared with when they are not going through exercise training. In addition, repeated exposure to social stimuli at the gym could have caused habituation to social fear and changes in social cognitions, thus helping in alleviation of SAD symptoms. This indicates that exercising in an anxious situation results in alleviation of anxiety symptoms (39). Moreover, exercising (improving one's physical health) can induce decrease of negative judgments and enhance kindness toward oneself (self-compassion). A previous study reported that exercise can improve anxiety through repeated exposure, improved self-efficacy, and distraction (40). A randomized controlled trial conducted to improve SAD reported that first-time use of aerobic exercise and group lessons for 8 weeks effectively alleviated severity of SAD. Similarly, findings from a previous animal study showed that aerobic exercise increased OT levels in female mice, alleviated anxiety, and increased empathy. Aerobic exercise combined with resistance exercise is an effective alternative to improve physical health and reduce cravings of drug-dependent people. Furthermore, aerobics combined with resistance training can significantly alleviate anxiety and depression associated with drug dependency (41). Moreover, it can improve aerobic exercise performance, muscle strength, and endurance, and promote recovery from drug dependence (42).

The present study had several limitations. For instance, the sample size was too small, and most of the participants withdrew from the study. The study sought to recruit and screen more subjects. However, in order to control the rigor of the research during the screening process, a population of 1,026 people were screened based on the standard of "heroin only;" thus, only one-third of the subjects were eligible. This resulted in inclusion of a smaller number of subjects in the study. Furthermore, the effect of the female menstrual cycle was not explored despite its potential effect on plasma OT levels (43–45). Peripheral blood OT level was determined in this study and not the central nervous system level. Previous animal studies report that the peripheral and central nervous systems are coordinated. Furthermore, plasma osmolality was not evaluated, which may affect plasma OT levels. DDQ and VAS scales were used to explore the craving degree to ensure the findings were accurate. However, this study lacks objectivity, owing to lack of objective indicators for strong demonstration. Although the preliminary experiments explored the clues that induce changes in blood pressure and heart rate during craving, these findings are not included in the study.

Although the relationship between OT level and SAD and heroin addiction has been extensively studied, only a few studies have explored the relationship between endogenous OT and the interaction between SAD and heroin addiction. Therefore, this is the first study to explore the effect of exercise in heroin addicts with SAD. The findings of this study indicate that adjuvant therapy, such as exercise, can improve the level of endogenous OT in drug withdrawal patients with SAD.

CONCLUSION

Plasma OT is a potential peripheral biomarker for prediction of severity of social anxiety in female heroin withdrawal Patients. Moreover, exercise can be used as an adjuvant therapy to increase the level of OT in heroin withdrawal patients and alleviate SAD and cue-induced craving.

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 Institutional Review Committee of Hunan Normal University approved. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW, JZ, LZ, and YG conceived and designed the experiments. JT, TH, and JL screened experimental subjects, signed the informed consent process, and conducted the exercise intervention. All authors contributed to the article and approved the submitted version.

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Predictors of Nutritional Status, Depression, Internet Addiction, Facebook Addiction, and Tobacco Smoking Among Women With Eating Disorders in Spain

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Eating disorders (EDs) are a complex group of psychiatric conditions that involve dysfunctional eating patterns, nutritional alterations, and other comorbid psychopathologies. Some women with EDs may develop problematic internet use while they attempt to get information on dieting/weight control or get online support from people with similar problems. They may also drift toward tobacco smoking as a method to regulate their weight or to cope with their weight-related dysphoria. The occurrence of these conditions in EDs may prolong disease course and impede recovery. This study used structural equation modeling to investigate nutritional status (noted by body mass index, BMI), depression psychopathology, internet addiction (depicted by the Internet Addiction Test), Facebook addiction (depicted by the Bergen Facebook Addiction Scale), and smoking among 123 Spanish women diagnosed with EDs (mean age = 27.3 ± 10.6 years). History of hospitalization, marital status, age, and the level of education predicted BMI in certain ED groups. BMI did not predict depression, but it predicted internet addiction, Facebook addiction, and smoking in certain ED groups. Depression did not predict BMI, internet/Facebook addition, or smoking in any ED group. Some sociodemographic and clinical variables had indirect effects on depression, internet addiction, and Facebook addiction while age was the only variable expressing a direct effect on all outcome measures. Age, education, and history of prolonged treatment predicted smoking in certain ED patients. The findings signify that a considerable target for interventional strategies addressing nutritional and addictive problems in EDs would be women with high BMI, history of hospitalization, history of prolonged treatment, who are particularly young, single, and less educated. Replication studies in larger samples, which comprise various subtypes of EDs from both genders, are warranted to define the exact interaction among the addressed variables.

Keywords: body mass index/BMI, depression psychopathology, eating disorders, Facebook addiction/internet addiction, nutritional status, Spain/Spanish, tobacco smoking, women

INTRODUCTION

Eating disorders (EDs) are a complex group of psychiatric conditions entailing dysfunctional eating patterns that are associated with other mental and physical symptoms (1–3). Genome-wide investigations report higher polygenic scores for body mass index (BMI) among patients with anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) (4). BMI is an indicator of nutritional status, which is obviously altered in EDs due to excessive dieting (e.g., underweight in patients with AN) or overweight/obesity due to excessive intake of calories in response to aversive environmental stimuli [e.g., in patients with BED and addictive eating disorders; (1, 4, 5)]. The latter involve less control over eating, frequent thinking about food, eating when not hungry, and even withdrawal-like symptoms when some foods (e.g., non-nutritive sugar and processed food) are not available (1). Frequent consumption of these foods is likely to increase the incidence of depression (6).

Depression is highly comorbid with EDs (7), and it occurs as a symptom of distress associated with discomfort about body shape and/or food consumption (2, 5, 8). Depressive symptoms in women with EDs also result from malnutrition/starvation as indicated by body weight, BMI, fat free mass index (FFMI), and serum level of beta-hydroxybutyric acid (2, 9, 10). Adipokines produced by fat tissue in obese individuals such as leptin stimulate the production of proinflammatory cytokines and free radicals resulting in a chronic general state of systemic inflammation and metabolic dysregulation (11, 12). As a result, brain injury (neuroinflammation and neurodegeneration) may develop, consequently triggering symptoms of depression (2, 12, 13). Weight restoration in women with AN is associated with a transient rise in depressive symptoms (9). In the meantime, large-scale data from UK Biobank denote an increased genetic susceptibility to high BMI in depressed individuals (14). Nonetheless, the interaction between BMI and dysphoric mood is complex entailing an interplay among several dietary, psychological, sociodemographic, and medication factors (2, 8, 13, 15–17).

While some EDs may have addictive eating demeanors (1), substance abuse is frequently comorbid in patients with EDs (7). Large-scale genome-wide studies report genetic association of EDs with substance abuse, depression, impulse control disorders, schizophrenia, and attention deficit hyperactivity disorder (4, 18, 19). University students who express symptoms of dysfunctional eating tend to exhibit excessive internet dependence (20). Patients with EDs may turn to digital interventions, which express efficacy comparable to that of face-to-face modalities (21), to keep anonymity. They may also refer to online patient groups to seek support, to learn acceptable ways for refusing food, and to share experiences conducive to weight loss, including some dangerous ways (22). Given the high prevalence of negative emotions (depression and anxiety) among patients with EDs (2), along with their genetic tendency toward the development of addictive disorders (4, 18, 19), individuals with EDs may shift toward internet addiction (20, 22)—repeated and uncontrolled use of the internet that causes deterioration of health, emotional negativity, poor impulse control, and maladjustment (23, 24). Depression, anxiety, and suicidal ideation are key correlates of problematic internet use (25). Thus, internet addiction may be a source of an extra emotional burden that furthers the deterioration of EDs by contributing to other addictive behaviors such as smoking. In fact, the literature associates internet addiction with tobacco smoking, heavy drinking, substance abuse, and sexual promiscuity in both genders, although at varying degrees (26–29). Negative emotions seem to be a core common effector in dysfunctional eating, internet addiction, and smoking (5, 17, 26, 30, 31).

Smoking rates are higher among women with EDs than in healthy control women (32). Smoking in EDs is associated with impulsive personality traits (32) and abuse of caffeine, alcohol, and marijuana (33). The literature spots a common association among eating behaviors, body weight, and smoking although the exact interaction between these first two variables and smoking is not well-defined (5, 34–36). While cigarette smoking may decrease appetite resulting in low BMI, some smokers tend to have high BMI and high waist circumference, indicating general and central obesity (5, 34). On the other hand, higher baseline BMI may trigger the initiation of smoking as an attempt to control or lose weight in some groups (35, 37). Analysis of data from UK Biobank and the Tobacco and Genetics (TAG) consortium ($N = 372{,}791$ and $N = 74{,}035$, respectively) shows that each SD increment in BMI increases the risk of being a smoker [odds ratio = 1.18, 95% CI 1.13–1.23, $p < 0.001$; (34)]. Smoking cessation is associated with weight gain probably due to increased caloric intake as a replacement of the smoking habit with food intake (34). Therefore, worries about gaining weight after smoking cessation may interfere with individuals' decision to quit smoking (35). The dynamics underlying the relationship between smoking and dysfunctional eating may be more complex than they seem to be. Imaging studies report abnormal activity of brain regions associated with self-referencing and emotional processing (e.g., medial prefrontal cortex and other brain regions) among smokers, AN and BN patients, and obese individuals who eat in response to aversive states (5, 30, 31, 38, 39). Psychopathological features closely linked to dysfunctional emotional processing are documented core correlates of internet addiction, smoking, binge drinking, substance abuse, problematic gambling, and maladaptive patterns of physical activity (26). A considerable attention should be paid to smoking among women since it is on the rise, especially in Europe (up to 38%) (40), and it is associated with increased incidence of metabolic disorders [e.g., diabetes mellitus; (41)], lung cancer (42), mortality (43, 44), and maternofetal complications when a smoker becomes pregnant (45). Based on the aforementioned background, the current study aims to identify the relationship between BMI and depression among women with EDs. It also hypothesizes that depression and BMI can predict internet addiction, Facebook addiction, and smoking in this patient group. These relationships are evaluated while taking into consideration the interaction of sociodemographic and clinical characteristics of the participants. **Figure 1** summarizes the relationships addressed in the current study.

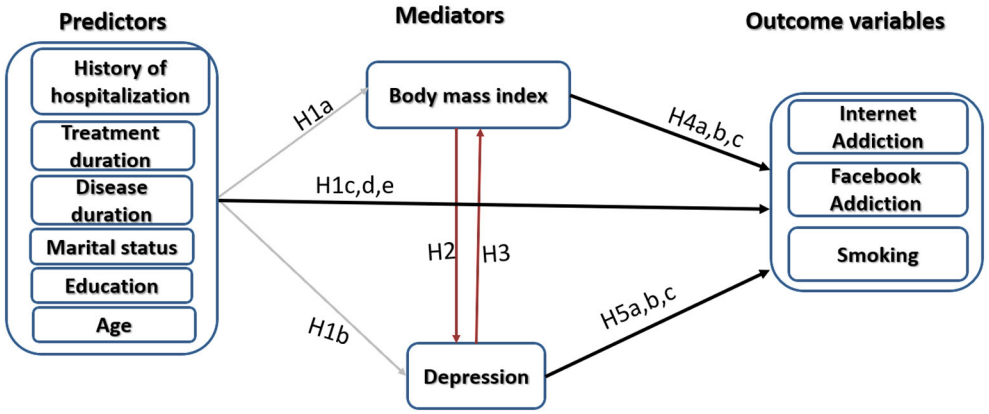

FIGURE 1 | Schematic illustration of the model used to test hypotheses of the present study. Hypothesis 1a (H1a): Sociodemographic and clinical characteristics contribute to altered body mass index in patients with EDs. Hypothesis 1b (H1b): Sociodemographic and clinical characteristics contribute to depression in patients with EDs. Hypotheses 1c, d, e (H1c,d,e): Sociodemographic and clinical characteristics contribute to internet addiction, Facebook addiction, and smoking in patients with EDs. Hypothesis 2 (H2): Altered body mass index contributes to depression in patients with EDs. Hypothesis 3 (H3): Depression contributes to altered body mass index in patients with EDs. Hypotheses 4a, b, c (H4a,b,c): Altered body mass index contributes to internet addiction, Facebook addiction, and smoking in patients with EDs. Hypothesis 5a, b, c (H5a,b,c): Depression contributes to internet addiction, Facebook addiction, and smoking in patients with EDs.

METHODS

Study Design, Participants, and Procedure

This cross-sectional study comprises a sample of 124 women recruited consecutively from the General University Hospital of Ciudad Real in Spain during the period between February and November 2018. Participants were included if they were aged above 12 years, were treated for EDs either at the outpatient or inpatient level, and were willing to sign an informed consent. Having cognitive impairment or physical disabilities disqualified participation in the study (22). The analysis is based on a de-identified publicly accessible dataset (46). Therefore, ethical approval has not been obtained for the current study.

Study Instruments

Data were collected through a self-administered questionnaire that consisted of three parts. Part 1 comprised a set of questions about participants' sociodemographic and clinical characteristics such as age, weight, height, ED diagnosis, disease duration, duration of being ever in treatment for EDs, history of hospitalization, psychiatric comorbidities, and smoking status.

The second part of the questionnaire comprised 20 items of the validated Spanish version of the Internet Addiction Test (IAT) (47). This scale was developed by Kimberly Young to measure problematic use of the internet. Items are rated on a 5-point Likert scale (1 = rarely, 2 = occasionally, 3 = frequently, 4 = often, and 5 = always) to depict the frequency of the symptoms. The total scores of the IAT range between 20 and 100; scores below 42 indicate normal use while higher scores indicate higher levels of internet dependence (24, 48, 49). The scale expresses sound psychometric properties including excellent internal consistency in the current sample (Cronbach's alpha = 0.99) (24).

The third part of the questionnaire comprised six items of the validated Spanish version of the Bergen Facebook Addiction Scale [BFAS; (50)]. Items of the scale identify problematic use of Facebook based on a score that ranges between 1 (very rarely) and 5 (very often). Problematic Facebook use can be detected at a total score of 12 or above based on a score of 3 on each of the six items of the BFAS (22). The internal consistency of the BFAS in the current study is excellent (Cronbach's alpha = 0.99).

Statistical Analysis

Because one response was missing, it was removed from the dataset resulting in a sample size of 123. We have used the overall score of the IAT and the BFAS in the statistical analysis. Both variables were tested for normality of distribution by Shapiro–Wilk and Kolmogorov–Smirnov tests of skewness and kurtosis. Descriptive statistics of non-normally distributed variables are reported as median (MD) and interquartile range (IQR) while numbers and percentages are used to describe dichotomous and categorical variables such as having a diagnosis of depression and smoking. Spearman's rho test was used to examine correlations. We created two groups of EDs: AN and other EDs. This is because AN was the most common diagnosis in the sample, and suboptimal body weight and low BMI were eminent features in this group. Meanwhile, other EDs were less presented, and BMI indicated overweight and obesity in patients with BN and BED; it was close to overweight in patients with EDs not otherwise specified. Therefore, these three conditions were grouped together (other EDs) to make subgroup analysis more informative. Between-group differences in sociodemographic and clinical variables were compared using independent sample t-test and χ^2-test, with bootstrap based on 1,000 random samples.

Normality testing revealed that the IAT and the BFAS were not normally distributed. Analyzing non-normal data derived from large samples by maximum likelihood (ML) and weighted least squares methods of estimation yields similar results—in terms

of overall fit and the discrepancy between estimated parameter values and the true parameter values used to generate the data (51). Therefore, we fitted the hypothesized structural equation (SEM) model using ML with bootstrap involving the generation of 2,000 random samples. We tested if the model fits differently in the two EDs groups through multigroup analysis. A non-significant χ^2 index was used to signify global model fit (24). Meanwhile, a good model fit was based on Comparative Fit Index (CFI) and Tucker–Lewis Index (TLI) equal to or above 0.95, and root mean square error of approximation (RMSEA) and standardized root-mean-square residual (SRMR) <0.06, although <0.08 was considered for an acceptable fit (13, 52).

Because ML model examining the predictors of smoking expressed poor fit, we created a Bayesian model to identify the distribution of the predictors of smoking. This is because smoking is a dichotomous variable (smoker, non-smoker). Bayesian modeling estimates the posterior distribution of parameters in question (predictors of smoking) as the mean of the distribution while uncertainties in these parameters are reported as credible intervals (CrI), which enclose 95% of the distribution of the potential predictors (44). A good model fit is judged by a posterior predictive *p*-value of around 0.5 and a symmetric 95% CrI centering close to zero (53). We created an initial model including depression, BMI, age, IAT, BFAS, marital status, education, years since diagnosis, years in treatment, and history of hospitalization as predictors. Because the posterior predictive *p*-value of this model was very low (0.00), indicating non-fit, most non-significant demographic and clinical variables were gradually eliminated until a good fit was obtained—at the point noting no further change in model fit, insignificant predictors (mainly BMI or depression) were retained. The analysis was conducted in SPSS and Amos version 24. Significance was considered at a probability of 0.05, two-tailed.

RESULTS

The current sample comprised 123 women with EDs; AN (N = 59, 48.0%), BN (N = 35, 28.5%), BED (N = 11, 8.9%), and eating disorders not otherwise specified (N = 18, 14.6%). The sociodemographic and clinical characteristics of the participants are reported in **Tables 1**, **2**. For all the sociodemographic and clinical characteristics, there were no statistically significant differences between patients with AN and patients with other EDs except for BMI $t_{(73.0)} = -6.77$, $p = 0.000$ and history of hospitalization $\chi^2_{(1)} = 34.56$, $p = 0.000$. Marital status and internet addiction showed a trend toward significance $\chi^2_{(1)} = 3.80$, $p = 0.051$; and $t_{(110.1)} = -1.94$, $p = 0.054$.

The non-significant χ^2 index of overall model fit resulting from ML with bootstrap analysis shown in **Table 3** indicates that the used models fitted the data on a global basis. Meanwhile, other absolute fit indices indicate good fit of the models tested in the samples. **Figure 2** displays the direct effects of predictor and mediator variables on BMI, depression, internet addiction, and Facebook addiction while **Table 4** shows the total effects, including indirect effects. For all patients, patients with AN, and patients with other EDs, in order, SEM models accounted for 31, 8, and 38% of the variances in BMI; 10, 5, and 16% of the variances in depression; 22, 31, and 21% of the variances in internet addiction; and 27, 30, and 28% of the variances in Facebook addiction (**Figure 2**).

TABLE 1 | Sociodemographic and clinical characteristics of the participants in the samples.

Participants' characteristics	Whole sample (N = 123) No (%)	AN (N = 59) No (%)	Other EDs (N = 64) No (%)
Age mean (SD) in years	27.3 (10.6)	25.8 (11.3)	28.7 (9.8)
Marital status◭			
Single	100 (81.3)	**52 (88.1)**	**48 (75.0)**
Married	22 (17.9)	**7 (11.9)**	**15 (23.4)**
Education			
Below high school	5 (4.1)	2 (3.4)	3 (4.7)
High school	78 (63.4)	41 (69.5)	37 (57.8)
University	40 (32.5)	16 (27.1)	24 (37.5)
Ever hospitalized			
Yes	63 (51.2)	**47 (79.7)**	**16 (25.0)**
No	60 (48.8)	**12 (20.3)**	**48 (75.0)**
BMI mean (SD)	22.2 (8.4)	**17.8 (2.6)**	**26.1 (9.7)**
Years since diagnosis MD (Q1–Q3)	8.0 (3.0–16.0)	7.0 (3.0–15.0)	9.0 (3.0–18.0)
Years of treatment MD (Q1–Q3)	6.0 (2.0–12.0)	6.0 (2.0–14.0)	6.0 (2.3–12.0)

AN, anorexia nervosa; ED, eating disorder; ◭, one observation is missing; BMI, body mass index; MD, median; Q1, first quartile; Q3, third quartile. Values in bold face are significantly different between groups.

As shown in **Table 4**, BMI predicted depression, internet addiction, and Facebook addiction in the whole sample. Its effect on internet addiction and Facebook addiction was marginal in both ED groups. Age predicted depression in the whole sample as well as BMI and depression in women with other EDs. It was the only sociodemographic variable that had a direct significant effect on internet addiction and Facebook addiction in all the samples. Education predicted depression in all the participants as well as BMI, depression, internet addiction, and Facebook addiction in women with other EDs. Its effect on the last two was indirect—mediated by BMI. Marital status predicted BMI in the whole sample. Depression had no effect on BMI (path trimmed), internet addiction, and Facebook addiction in all the samples.

To examine if this basic model significantly varies between patients with AN and patients with other EDs, we ran multigroup analysis involving both groups. Multigroup analysis indicates overall agreement of the tested model across ED groups. However, constraining regression weights, covariances and residuals to equality between groups considerably reduced model fit (**Supplementary Material**). Some significant effects noted in the whole sample were insignificant in one or both groups due to several between-group variations in the shared group means of BMI, internet addiction, and Facebook addiction as

TABLE 2 | Descriptive statistics of internet addiction, Facebook addiction, smoking, and depression in the samples.

Key variables	Whole sample (*N* = 123)		AN (*N* = 59)		Other EDs (*N* = 64)	
	MD	Q1–Q3 (IQR)	MD	Q1–Q3 (IQR)	MD	Q1–Q3 (IQR)
IAT	16	5–35 (30)	15	4–33 (29)	16.5	5–54 (49)
BFAS	33	23–60 (37)	34	24–50 (26)	32	23–70.8 (48)
Smoking no (%)	56	45.5%	23	39.0%	33	51.6%
Depression no (%)	36	29.3%	15	25.4%	21	32.8%

AN, anorexia nervosa; ED, eating disorder; IAT, Internet Addiction Test; BFAS, Bergen Facebook Addiction Test; MD, median; Q1, first quartile; Q3, third quartile; IQR, interquartile range.

TABLE 3 | Fit indices of the tested basic model in the samples.

Samples	χ^2	*df*	*p*	CFI	TLI	RMSEA	SRMR
Whole sample (*N* = 123)	9.570	9	0.386	0.998	0.995	0.023	0.0489
AN (*N* = 59)	12.437	9	0.190	0.970	0.908	0.081	0.0837
Other EDs (*N* = 64)	4.582	9	0.869	1.000	1.069	0.000	0.0414

AN, anorexia nervosa; ED, eating disorder; χ^2, chi-square; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker–Lewis Index; RMSEA, root mean square error of approximation; SRMR, standardized root mean residual.

well as regression weights of marital status and age in the paths predicting depression and BMI (**Supplementary Material**).

As for predictors of smoking in the participants, the tested Bayesian models fitted data properly in all the samples as noted by posterior predictive values close to 0.5. As shown in **Table 5**, age was the only significant sociodemographic predictor of smoking in the whole sample while age and education were significant predictors of smoking in patients with AN. BMI predicted smoking only in patients with AN. On the other hand, neither age nor BMI predicted smoking in patients with other EDs. Depression was not a significant predictor of smoking in all the samples (paths trimmed in the whole sample and other EDs group), and mediation analysis showed no indirect effects of age or BMI on smoking via depression in patients with AN (-0.001 ± 0.000, 95% CrI: -0.017 to 0.012 and -0.015 ± 0.000, 95% CrI: -0.095 to 0.042, respectively). Years in treatment and chronicity (years since diagnosis) predicted smoking in the whole sample and in patients with other EDs.

DISCUSSION

This study investigated the predictors of BMI and if BMI predicts depression among patients with EDs. It also examined the possible effects of BMI and depression on problematic use of the internet and Facebook as well as tobacco smoking, taking into account the effect of some of the confounding factors reported in the literature. Sociodemographic and clinical characteristics, not depression, predicted BMI. BMI was not associated with depression, but it was associated with internet addiction, Facebook addiction, and smoking in certain ED groups. Depression did not predict BMI, internet/Facebook addition, or smoking. Some sociodemographic and clinical factors had indirect effects on depression, internet addiction, and Facebook addiction while age was the only variable expressing a direct effect on internet addiction and Facebook addiction. Age, education, and few clinical characteristics predicted smoking in certain ED patients.

History of hospitalization and marital status predicted BMI in the whole sample while age and education predicted BMI in patients with other EDs. These findings are consistent with those of previous reports. In this regard, BMI in hospitalized patients with AN increased from admission to discharge, which was likely to be explained by lower admission BMI and longer inpatient stay (54). BMI $\geq$19 kg/m^2 at hospital discharge is associated with five-fold higher BMI restoration in women with AN (55). A study investigating the clinical impact of marital status on ED symptomatology suggests that ED patients who live with a partner are significantly older and demonstrate significantly higher levels of purging behavior than non-cohabiting counterparts (56). Our study supports this report as indicated by a significant correlation between being ever hospitalized and marital status ($r = -0.284$, $p = 0.000$), denoting the presence of a considerably strong association between ED psychopathology and marital status. In line with our findings, obesity in patients with EDs is reported to be common among individuals who have only primary education—mostly patients with BN and BED (57).

In the whole sample and patients with other EDs, age, and education were significant predictors of depression while marital status was a marginal predictor. History of hospitalization predicted depression in the whole sample, but this effect vanished in either ED groups. Consistent with our findings, Anker et al. reported lower prevalence of depression and addictive disorders in ED patients with education above high school level (>12 years) (58). Women with chronic AN (disease chronicity >7 years) tend to be more depressed than short-term patients; they also are older and have more previous hospital admissions (55).

In this study, BMI predicted depression in the whole sample, but this effect was not noticed in either ED groups. Overeating usually occurs in response to negative emotions,

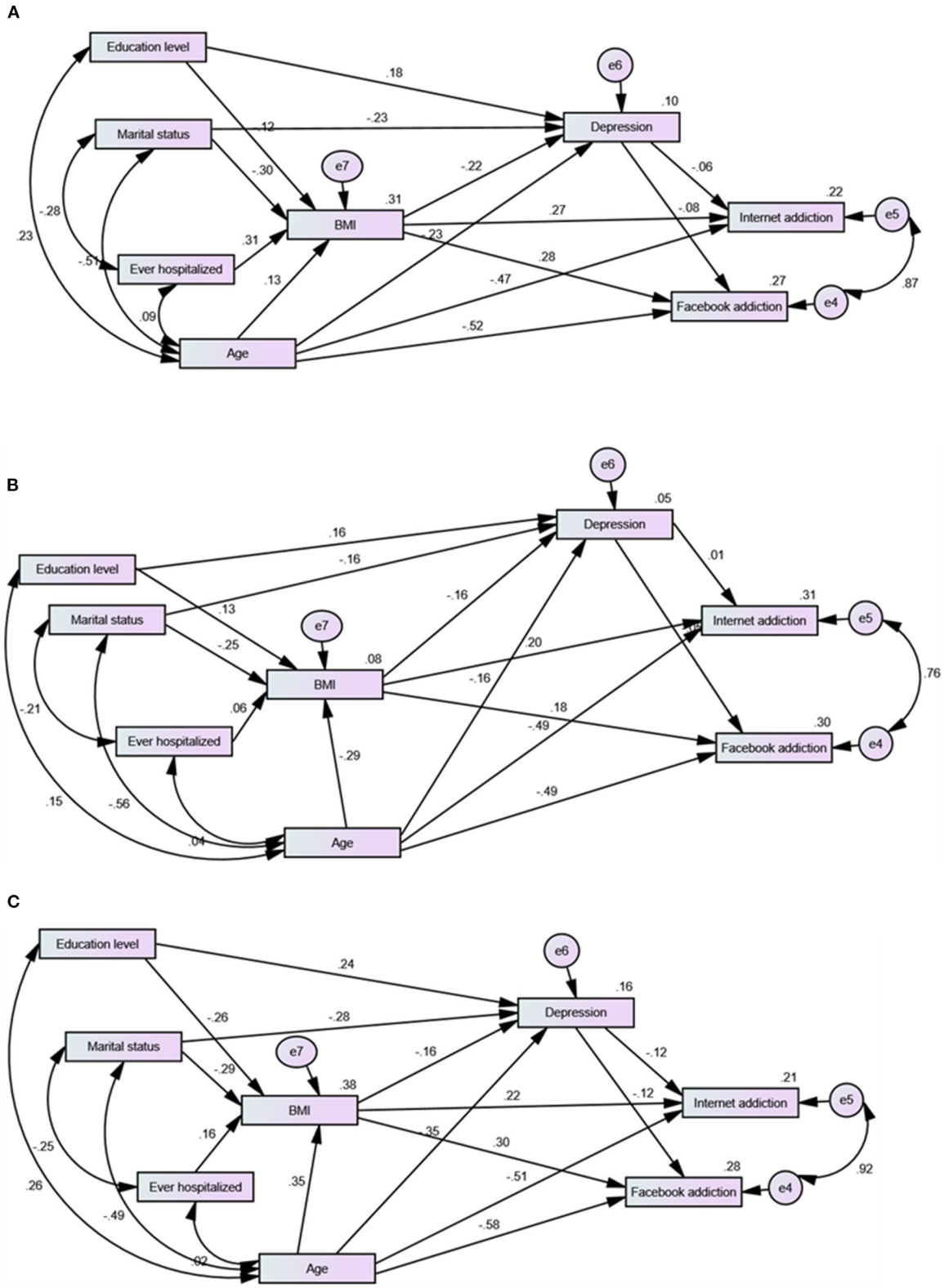

FIGURE 2 | Direct effects from structural equation model predicting depression, internet addiction, and Facebook addiction among women with different eating disorders **(A)**, with anorexia nervosa **(B)**, and with other eating disorders **(C)**.

TABLE 4 | Standardized regression weights of the total effects of predictors of internet addiction and Facebook addiction along with *p*-values and 95% confidence interval.

Predictors	Samples	Outcome variables											
		Body mass index			Depression			Internet addiction			Facebook addiction		
		β	*p*	95% CI	β	*p*	95% CI	β	*p*	95% CI	β	*p*	95% CI
Education	*N* = 123	−0.117	0.194	−0.294 to 0.055	0.209	**0.022**	0.031 to 0.369	−0.044	0.131	−0.123 to 0.015	−0.050	0.108	−0.133 to 0.010
	N = 59	0.127	0.392	−0.153 to 0.401	0.144	0.310	−0.113 to 0.331	0.027	0.385	−0.039 to 0.143	0.015	0.622	−0.058 to 0.130
	N = 64	−0.263	**0.036**	−0.502 to −0.016	0.280	**0.041**	0.016 to 0.502	−0.092	**0.035**	−0.217 to −0.006	−0.114	**0.022**	−0.254 to −0.015
Marital status	*N* = 123	−0.296	**0.040**	−0.525 to −0.010	−0.170	0.067	−0.353 to 0.017	−0.069	0.092	−0.162 to 0.013	−0.067	0.117	−0.160 to 0.018
	N = 59	−0.255	0.104	−0.614 to 0.049	−0.121	0.418	−0.414 to 0.223	−0.053	0.116	−0.172 to 0.017	−0.039	0.248	−0.155 to 0.034
	N = 64	−0.289	0.154	−0.571 to 0.096	−0.236	0.085	−0.498 to 0.048	−0.037	0.410	−0.175 to 0.075	−0.058	0.310	−0.188 to 0.069
Ever hospitalized	*N* = 123	0.311	**0.001**	0.167 to 0.448	−0.068	**0.022**	−0.163 to −0.007	0.087	**0.002**	0.029 to 0.173	0.091	**0.001**	0.033 to 0.180
	N = 59	0.058	0.505	−0.121 to 0.244	−0.009	0.363	−0.084 to 0.014	0.012	0.374	−0.019 to 0.079	0.011	0.351	−0.016 to 0.077
	N = 64	0.155	0.143	−0.050 to 0.345	−0.025	0.216	−0.145 to 0.010	0.037	0.116	−0.008 to 0.127	0.050	0.120	−0.011 to 0.146
Age	*N* = 123	0.135	0.229	−0.082 to 0.347	−0.259	**0.022**	−0.469 to −0.038	−0.422	**0.001**	−0.542 to −0.291	−0.461	**0.001**	−0.580 to −0.326
	N = 59	−0.294	0.093	−0.581 to 0.055	−0.111	0.520	−0.492 to 0.256	−0.554	**0.002**	−0.669 to −0.397	−0.540	**0.001**	−0.677 to −0.362
	N = 64	0.350	**0.019**	0.048 to 0.620	−0.406	**0.004**	−0.670 to −0.108	−0.384	**0.001**	−0.575 to −0.196	−0.425	**0.000**	−0.617 to −0.246
BMI	*N* = 123	–	–	–	−0.217	**0.027**	−0.445 to −0.022	0.279	**0.003**	0.093 to 0.442	0.294	**0.002**	0.114 to 0.460
	N = 59				−0.156	0.254	−0.405 to 0.114	0.202	**0.037**	0.011 to 0.383	0.185	0.095	−0.033 to 0.387
	N = 64				−0.158	0.274	−0.515 to 0.124	0.241	0.057	−0.009 to 0.469	0.322	**0.011**	0.075 to 0.532
Depression	*N* = 123	–	–	–	–	–	–	−0.059	0.474	−0.229 to 0.103	−0.084	0.330	−0.250 to 0.083
	N = 59							0.009	0.913	−0.0215 to 0.224	−0.051	0.741	−0.288 to 0.198
	N = 64							−0.117	0.308	−0.344 to 0.102	−0.125	0.281	−0.348 to 0.096

N = 123, whole sample; N = 59, anorexia nervosa sample; N = 64, other eating disorders sample; β, standardized total parameter estimates. Boldface values indicate significant findings.

TABLE 5 | Predictors of smoking among the samples indicated by posterior probabilities from Bayesian modeling.

Predictors	Whole sample ($N = 123$)				AN ($N = 59$)				Other EDs ($N = 64$)			
	Mean	SD	p▲	95% CrI	Mean	SD	p▲	95% CrI	Mean	SD	p▲	95% CrI
Depression	–	–	–	–	0.325	0.308	0.46	−0.149 to 0.990	–	–	–	–
BMI	–	–	–	–	0.182	0.086	0.46	**0.024 to 0.361**	0.000	0.019	0.45	−0.036 to 0.037
Age	0.049	0.021	0.47	**0.008 to 0.092**	0.040	0.019	0.46	**0.003 to 0.079**	–	–	–	–
Level of education	0.204	0.123	0.47	−0.037 to 0.447	0.578	0.215	0.46	**0.164 to 1.007**	–	–	–	–
Years in treatment	0.855	0.309	0.47	**0.257 to 1.474**	–	–	–	–	0.258	0.091	0.45	**0.091 to 0.436**
Years since diagnosis	−0.120	0.046	0.47	**–0.210 to –0.032**	–	–	–	–	−0.179	0.072	0.45	**–0.328 to –0.048**

AN, anorexia nervosa; ED, eating disorder; ▲, posterior predictive p; 95% CrI, 95% credible interval. Boldface values indicate significant finding.

and it contributes to obesity in some EDs such as BED (5). BMI correlates with suicidality (commonly associated with depression) in male and female patients with EDs, and this effect is aggravated by binging behavior (59). Pleplé et al. have shown an association between indicators of nutritional status (BMI and FFMI) and psychopathology (anxiety and depression) in hospitalized patients with AN. However, that association was confounded by psychotropic medications (antidepressant, anxiolytic, and neuroleptic drugs). These drugs were associated with lower FFMI at discharge, and FFMI was significantly associated with the severity of anxiety and depressive symptoms in these patients (2). Lower lifetime BMI in chronic patients with AN is associated with greater levels of depression and neuroticism than short-term patients (55). Therefore, the association between nutritional status and depression in EDs may be better investigated with regard to emotional dys/regulation, psychiatric treatment, and disease chronicity, which were all missing in the current study.

BMI predicted internet/Facebook addiction in all the samples, although its effect was marginal in both ED groups (**Table 4**). Consistent with our results, BMI is reported to be associated with internet addiction among adolescents, independent of ED subtype, age, and sex (60–62). However, one study reported no association between age, sex, and BMI with internet addiction among adolescents (27). The association between BMI and internet addiction may be explained by physical inactivity associated with prolonged internet use (>3 h) (60, 63, 64). Frequent snacking during use time may also affect BMI in individuals with internet addiction (60). This observation may hold true given the high prevalence of disordered eating attitudes evaluated by the Eating Attitude Test-26 (61) and disordered eating evaluated by the Eating Disorder Inventory among adolescents and college students with problematic internet use (20). In fact, prolonged computer use is associated with increased eating while not hungry, which promotes the build-up of excess body fat mass (64).

Young age predicted internet/Facebook addiction in all the samples, which is in accordance with several studies (17, 20, 65–67). Age seems to be a key factor in EDs. Among men and women, age demonstrates inverse linear associations with both restrictive and bulimic EDs, highlighting 18–25 years as the most vulnerable period (68). Age is also an important variable that correlates with several personality traits and behaviors. Young age is associated with lower educational level, which predicted internet/Facebook addiction in patients with other EDs. This finding is consistent with a former study reporting education as a confounding factor in neuropsychological alterations in individuals with BED (69). In our study, young age (commonly associated with being unmarried) negatively correlated with marital status ($r = -0.524$, $p < 0.001$), which marginally predicted depression and internet addiction in the whole sample. In harmony with this finding, university students who did not fall in love or failed their love relations were more likely to be Facebook dependent than students in love relations (66). Likewise, young Polish single women and women with higher scores on the De Jong Gierveld Loneliness Scale are reported to display the highest level of depressive symptoms and dependence on the internet and Facebook than older and married women (17). Likewise, internet addiction has a significant negative correlation with social support among university students (28). Altogether, young age, which entails high vulnerability to EDs, is associated with less education and being single/lonely, which may increase vulnerability to internet addiction.

In the current study, having a diagnosis of depression had no contribution to BMI, smoking, or problematic use of the internet and Facebook. In line with our findings, a cross-lagged panel study reported a moderate positive association between depression and internet addiction at different time points. However, in cross-lagged analysis, this association disappeared giving room to loneliness—which develops over time as a drawback of prolonged internet use—as a major predictor of internet addiction (63). In that study, online contact with family and friends could not prevent the development of loneliness associated with internet addiction (63). Facebook addiction is reported to be significantly higher in psychiatric inpatients with mild depression than in those with moderate depression (70). On the contrary, depression is reported to positively associate with Facebook addiction (66) and to partially mediate the relationship between internet addiction and weight change, weight concern, and binge eating among university students (20). Depressive and anxiety symptoms, and suicidal ideation are linked to excessive use of the internet in another sample of university students (25). Moreover, the literature shows that having a major depressive episode increases the risk for smoking and continued smoking

in pregnant women (71). Likewise, analysis adjusted for age and gender shows that emotional dysregulation in smokers aggravates emotional eating resulting in increased BMI (5). The observed lack of associations between depression and other outcome variables in the present study may be attributed to the use of depression as a diagnosis rather than a symptom. Depression is a self-remitting disease—acute major depression regresses to the mean and improves spontaneously (72). The contribution of symptoms of depression or anxiety to dysfunctional behaviors goes far beyond having a diagnosed disease of depression or anxiety (16, 73). Cumulative knowledge associates symptoms of emotional negativity (anhedonia, negative affect, and low positive affect) with increased smoking risk, craving, and relapse although they demonstrate mixed or no relationship with smoking heaviness, chronicity, and nicotine dependence (74). These symptoms are not stable in people diagnosed with depression due to spontaneous recovery (72), while emotional symptoms of depression can alter psychosocial functioning (75). Longitudinal data show that depression severity was a key predictor of internet addiction among university students, especially younger students (65). In adjusted analysis, spontaneous remission of problematic internet use in adolescents was only predicted by lower levels of maladaptive emotion regulation strategies (76). Specific psychopathological features, including those occurring in depression (anhedonia and alexithymia) and those embroiled in emotional dysregulation such as dissociative proneness, are key correlates of binge drinking, problematic gambling, internet use, and physical exercise addiction among Italian adolescents (26). Therefore, absence of assessment of the severity and affective dimensions of depression as well as aspects of emotional dysregulation that contribute to depression in the current study disqualified the contribution of depression to BMI, tobacco smoking, and internet/Facebook addiction in the current study.

In our analysis, higher BMI, independent of depression, was a significant predictor of smoking only among patients with AN. This result indicates that smoking might be adopted as a weight control measure in this group of patients, which is in accordance with the available literature (35, 37). Observational studies show that higher BMI and body dissatisfaction in adolescent females are associated with increased odds of early onset regular smoking (36). Mendelian randomization analyses based on data from UK Biobank and the TAG consortium denote a causal effect of higher BMI on lifetime smoking, initiation of smoking, smoking heaviness, and DNA methylation at the aryl-hydrocarbon receptor repressor locus, but it has no effect on smoking cessation (34, 37). Smoking cessation plans were numerically higher in normal BMI Korean smokers than in underweight, overweight, or obese age- and gender-matched counterparts, although the difference was not significant (35). Other factors may affect smoking cessation such as high-risk drinking, levels of physical activity, and health problems [e.g., hypertension; (35)]. The contribution of these factors to smoking in patients with EDs is worthy of investigation in future studies.

In our study, smoking tended to be higher among older patients with all EDs and AN. In line, a meta-analysis reports that smoking rates are higher among adult, pregnant, and diseased women than in adolescent girls (40). In accordance, projection studies based on Spanish National Health Surveys (2003, 2006, and 2011) predict a significant decline in smoking rate among young Spanish women and a significant increase in smoking rate among older women (44). The level of education predicted smoking only in women with AN. This finding is consistent with the literature, which associates low educational levels with higher levels of smoking in EDs (68), other psychiatric conditions (77, 78), and even in healthy individuals (71).

Binge/purging subtype of AN as well as EDs characterized by excessive eating express genetic variability in dopamine D4 receptor (DRD4) (79, 80). DRD4 regulates reward response in different brain regions (e.g., prefrontal cortex) in drug addiction, food craving, and overeating. DRD4 mutations involving the 7R allele are associated with heavy smoking, higher craving, less dopamine release in the ventral caudate after smoking, less likelihood to smoking cessation, and greater reactivity to smoking-related cues in ex-smokers (79). It seems that genetic variability in DRD4 accounts for increased tendency for smoking among EDs, especially AN. In fact, nicotine vaping for 30 days among American university students ($N = 51{,}231$) is associated with increased self-reported lifetime EDs (all subtypes, 3.7%) and elevated ED risk (25.0%) (81). Another investigation of EDs among community-dwelling women with comorbid alcohol use disorder and nicotine dependence ($N = 3{,}756$, median age = 22 years) revealed that AN is the most prevalent disorder among these women (relative risk ratio, RRR = 3.17; 99% CI: 1.35–7.44) followed by purging disorder (RRR = 2.59; 99% CI: 1.24–5.43) and various symptoms of EDs (82). A similar investigation among individuals diagnosed with substance use disorder revealed a higher prevalence of food addiction than in the general population, especially among young women with high BMI (83). Although there was no significant association with any specific substance, the highest prevalence noted, in order, was among users of cannabis (31.03%), heroin (21.07%), cocaine (18.53%), alcohol (14.49%), and tobacco (11.61%) (83). Subchronic administration of the natural CB1/CB2 receptor agonist Δ9-tetrahydrocannabinol, found in cannabis, to rat models of activity-based AN can significantly reduce plasma corticosterone, weight loss, restrictive eating behavior, and running wheel activity (84). Involvement of the cannabinoid system in AN may also account for the high comorbidity of addictive disorders among AN patients, probably as an attempt for self-medication. Nonetheless, the present study did not properly assess the type of smoking (e.g., cigarette smoking vs. vaping) neither the intake of cannabis and other illicit drugs—a limitation in need to be addressed in future studies.

Chronicity was a negative predictor of smoking while being in treatment for a long time positively predicted smoking, especially in women with other EDs (**Table 5**). ED patients in prolonged treatment are likely to have a severe disease course with higher emotional eating, which may be associated with higher smoking (5). This logic is consistent with the fact that women with BN and binge/purge report the highest rates of smoking among all the subtypes of EDs (32, 33). ED patients receive antidepressant, anti-anxiety, and psychotropic drugs, which alter body composition and mood (2), in addition to modulating the cholinergic–nicotinic and dopaminergic systems (78). Therefore, smoking

may be related to the neurobiological interactions induced by psychotropic medications while in prolonged treatment. In line with this argument, smoking and the use of hypnotic medications are frequently reported in individuals with nocturnal eating behavior and sleep-related eating disorder–like behavior, which express features consistent with bulimic and binge EDs (85). Likewise, adjusted analysis strongly relates smoking to the intake of psychotropic drugs in patients with schizophrenia (78). On the other hand, smoking may contribute to prolonged disease course because it causes interindividual variations in response to drug treatment. This is because the polycyclic aromatic hydrocarbons present in cigarette smoke induce hepatic aryl hydrocarbon hydroxylases resulting in higher metabolic clearance of substrate drugs for these enzymes (e.g., psychotropic and antidepressant drugs). As a result, biotransformation rates and plasma concentrations of these drugs decrease (86). This hypothesis may hold true given the cross-sectional nature of the current study, and it may be worth investigating in future studies.

In this study, smoking was not associated with internet addiction or Facebook addiction ($r = 0.000$ and -0.016, $p > 0.05$)—these paths were insignificant, and thus were trimmed in ML and Bayesian models to improve model fit. This finding is consistent with those of a study reporting marginal associations between Facebook/internet addiction and smoking or substance abuse in university students in Bangladesh (66). However, this result is contradictory to other studies reporting associations between smoking and internet addiction (26, 27, 29). It is not clear why the findings on the associations between smoking and internet addiction are mixed. However, this difference may be considered within the frame of desire frequency and strength for smoking reported by Hofmann et al. (87). Although smoking is addictive, they found that the averages of desire frequency and strength for smoking among adults are much lower and less conflicting than those for the desire for social media use. The latter were more likely to be enacted despite resistance (87). Nonetheless, studies are needed to investigate such a possibility.

This study has investigated several aspects of pathology in EDs: nutritional status, depression, internet addiction, Facebook addiction, and smoking. However, the generalizability of the findings of the current study may be limited by the cross-sectional design, inclusion of females only, single-clinical setting, unpowered and purposive sample, less representation of different subtypes of EDs, absence of assessment of negative affect, and possible social desirability bias. Internet/Facebook addictions were self-reported instead of being evaluated based on standard criteria of behavioral addiction described in common disease classification systems. It was not possible to evaluate many other key relations because of absence of various smoking-related variables (e.g., frequency, duration, vaping vs. cigarette smoking, age of initiation, use of smoking as a weight control strategy, taking part in smoking cessation programs, number of quitting trials, and relapse history). Moreover, relevant clinical characteristics of the sample were missing such as how the diagnosis of depression was established, presence of medical comorbidities and other addictive behaviors (e.g., alcohol and substance use), family history of psychiatric disorders, details of treatments (medications and psychotherapy) received by the participants, body dissatisfaction, and level of physical activity. In addition, absence of assessment of the key outcomes in age-cross-matched healthy control women in the present study may cast doubt on the possibility that the findings are specific to women with eating disorders. Replicating the study in larger samples, which comprise various subtypes of EDs from both genders, along with a healthy control group may be necessary to define the exact interaction among the addressed variables.

CONCLUSION

This study highlights the contribution of age to BMI, depression, internet/Facebook addiction, and smoking in women with EDs. BMI contributed to internet/Facebook addiction and smoking in certain ED groups, but depression did not contribute to any of these variables. The level of education and history of hospitalization or prolonged treatment were associated with internet/Facebook addiction and smoking in certain ED groups. Given the devastating effects of co-morbid addictive behaviors on the disease course in EDs, early identification of addictive behaviors in highly prone ED patients becomes of specific importance. Empirical evidence documents positive effects of cognitive behavioral therapy (CBT) on internet addiction, anxiety, impulsivity, and social avoidance (88). For these conditions, CBT in combination with electro-acupuncture is more effective than CBT alone. Together, they increased the amplitude distance S1P50 and S2P50 of Auditory Evoked Potential, denoting that these interventions improve internet addiction symptom by increasing cerebrum sense perception gating function (89). Our findings pinpoint that interventional strategies targeting addictive behaviors in women with EDs may lead to promising results in young age, high BMI, single, and less educated groups.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Mendeley (https://data.mendeley.com/datasets/d5z2bnnv65/1).

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because the analysis is based on a publicly available dataset. We are referring to the original study and dataset in our manuscript. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AMA and HK conceptualized the topic. YK and HH acquired fund. AMA and HH conducted the statistical analysis and

wrote the first draft of the article. HK and YK reviewed and edited the article. All authors have approved the final version of the article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.735109/full#supplementary-material

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Prevalence and Differences of Depression, Anxiety, and Substance Use Between Chinese College-Age Students Studying in China and America During the Coronavirus Disease 2019 Pandemic

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Introduction: The coronavirus disease (COVID-19) swept the globe and harmfully influenced the mental health and behaviors of the college student population. This study aims to examine the prevalence and difference of mental health and the substance use problems of the Chinese college-age students studying in China and America (CSA) during the COVID-19 pandemic.

Methods: One thousand five hundred four students participated in this study. A total of 42.12% of students are enrolled in Chinese colleges, and 57.78% of students are enrolled in American colleges, aged 17–23 years ($\bar{x} \pm s = 19.90 \pm 1.50$). Binary logistic regression and independent *t*-test were used in this study to find the predictor variables and association among mental health, substance use problems, and student population.

Results: The two student groups had a statistical difference in General Anxiety Disorder-7 scale, alcohol, medicines, drinks, drugs and cigarettes ($p < 0.01$). The students suffering depression problems from the two groups have statistical significance with drinks (odds ratio = 0.89, 95% confidence interval = 0.81–0.97, $p < 0.05$; odds ratio = 1.11, 95% confidence interval = 1.04–1.19, $p < 0.01$). CSA experiencing anxiety problem had a significant association with alcohol, drinks, cigarette, and desserts ($p < 0.05$).

Conclusion: This is the first cross-sectional study focusing on the comparison of the Chinese college-age students' mental health and substance use problems who are studying in China and America during the pandemic. Our study revealed severe mental health and substance use problems in both student groups, particularly in the CSA during the COVID-19 pandemic. The findings of our study also highlight the evidence to find more interventions and preventions to solve the different mental health and substance use problems for college students.

Keywords: anxiety, depression, substance use, college students, COVID-19

INTRODUCTION

The outbreak of health emergencies resulting from coronavirus disease 2019 (COVID-19) not only negatively impacted the mental and physical health of the general population but also increased the incidence of psychological crises (1, 2). A growing literature revealed that many individuals were experiencing severe psychological burden during this period across countries (3–6); stressors involve social isolation, health concerns, fears of being infected, and stigma, which resulted in a series of negative emotional problems, fear, anxiety, and frustration.

Most college students are in the phase of stepping into their adulthood and are usually under tremendous pressure from academic and social lives due to most of them are living independently for the first time (7, 8). Xiang et al. found that the educational environment changes could lead them to increase stress and perform poorly, influencing their cognition and motivation and generating feelings such as fear and anxiety, especially during the pandemic. According to the previous research report, during the COVID-19 pandemic, Chinese college students' anxiety and depression levels were higher than the national norm level (9–11). The lockdown of schools caused by the COVID-19 pandemic created a significant negative impact on these students' mental health and substance use, which have entirely changed their academic and social life across the countries (3, 4, 7). Chinese domestic college students were at high risk of common mental health problems, such as depression, anxiety, and substance use problems (9, 10).

Although the Chinese college students studying in China (CSCs) were significantly impacted by the COVID-19 pandemic, the Chinese international college students in America (CSAs) have also been influenced negatively. Most educational institutions were shut down in mid-March in 2020 in the United States, and all students were forced to shift their classes into the remote model *via* Zoom and Google Meet (12), which led most of these international students to go back to China. The alternation of the teaching model and the huge time difference resulted in anxiety, and sad feelings for these students have emerged during the pandemic. Furthermore, the COVID-19 pandemic caused these students to be not able to attend commencement in person but to take a semester/year gap or transfer back to Chinese colleges. They also had to stop working on their internships and research projects (13, 14). For social lives, many racist and violent reports in the TV and news have significantly increased and escalated against Asians, including Chinese in America, because the first case was reported in China. It is reported that Chinese international students have experienced these negatively biased and perceived discriminations and anxiety during the period (15–17). A profound long-term negative influence, such as depression and anxiety levels, has changed Chinese college students' experiences in America (5). Against this background, we want to find the difference between CSC and CSA by analyzing the prevalence of mood disorders and substance use problems to provide evidence for the prevention and clinical treatment of mental health problems of the college students' population. Furthermore, considering that COVID-19 is a global challenge that impacts college students' mental health globally, it is also urgent to obtain information regarding the problems in different countries caused by the pandemic and potential factors that can influence its extent in different countries.

In addition to mental health problems, substance use problem is also becoming a severe issue among the college student population and is closely associated with mental health. The previous study reported that college students formed a large proportion of binge drinkers among young generations, and 70% of American college students were drinkers in 2007 in the United States (18, 19). At the same time, cigarettes have similar results, with a marked increase in smoking rates among people with a high level of education, college students, in China. A total of 53% of the Chinese participants in a study reported having smoked during their college (20, 21). The non-medical use of prescription drugs (NMUPD) is also a health issue among college students. It was previously reported that college students have a high prevalence of NMUPD in the United States, whereas it also concluded that NMUPD in Chinese college students appears to be common recently (22). Besides, over 90% of students reported buying coffee and energy drink almost every day (23, 24). The recent studies also indicated that the college students' substance use situation, including alcohol, cigarette, and marijuana (25–27), was more frequent and severe than before the pandemic. Thus, it is also emergent and important to examine how substance use has changed during the pandemic and how it could relate to mood disorders to give evidence in solving the future problems of mental health and substance abuse among college students.

To facilitate the development of domestic and international college students' mental health and substance use intervention programs, we need a better understanding of both the epidemiology of depressive and anxiety symptoms and substance use in CSC and CSA amid the COVID-19 pandemic. Although many researchers are investigating these issues in CSCs, the research of CSAs is limited. To better help policymakers and psychologists on this issue, this study analyzes and compares prevalence in mental health by taking the sample from CSC and CSA during the COVID-19 pandemic. The hypothesis of the present study is that both CSCs and CSAs will experience mood problems, depression, and anxiety. Based on a previous study (5), CSAs would experience more severe mood and substance abuse problems than those studying in China during the pandemic. The students in America are expected to experience more frequent alcohol and drug use problems than students in China. The findings of our study could give some evidence for establishing culturally tailored prevention intervention programs to provide a direction for solving the mental health and substance use of college students, even extend to all college students across the world to decline the risk of future public health emergencies.

METHODS

Participants

As approved by the Denison University and Zhejiang Provincial People's Hospital's Institutional Review Board, the authors developed and released an online and anonymously survey on the official website of "Questionnaire Star," a professional

online questionnaire and evaluation platform. Participation was voluntary, and their responses to this survey would be truly anonymous, which means that it ultimately ensures that no one could ever identify their responses to who they are.

To recruit the student participants, we published an online questionnaire on the website of "Questionnaire Star" and spread it into social media. One thousand six hundred forty-five participants were collected through social media and the website of "Questionnaire Star." Questions such as present location, study model (hybrid/in-person/remote/gap), highest education, and class year were asked before answering the survey to recruit the student participants. We excluded (1) participants who still live in America during the collecting period to make all student participants experience a similar environment, to diminish errors; (2) those whose age does not fit the undergraduate school range; (3) participants who do not fully complete the questionnaires; (4) students who are taking a semester/year gap; and (5) students who are not presently enrolled in college. As a result, 1,504 students participated in this study and were distributed to the CSC group ($n = 635$) and the CSA group ($n = 869$). There were 42.15% men and 57.85% women, and the age range is from 17 to 23 years ($\bar{x} \pm s = 19.90 \pm 1.50$).

Measures

The online survey is divided into four main sections, and the specific items and scores are shown in Tables, including the demographic questions (age and sex), Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 scale (GAD-7), and substance use questions. The PHQ-9 is a self-rating survey of the diagnostic instrument for common mental disorders, which showed good reliability and validity in a previous study (28). The GAD-7 is a seven-item anxiety survey that had good reliability, as well as an internal, criterion, construct, current, and convergent validity (29). The substance use scale was designed by our research team and assessed the participants' frequency of substance use per week, such as alcohol (beer, whiskey, etc.), medicines (sleeping pills, dietary supplements, etc.), desserts (cake, ice cream, etc.), drinks (coffee, bubble tea, etc.), drugs (marijuana, nitrous oxide, etc.), cigarettes (tobacco, e-cigarette, etc.), and snacks (Chex Mix, pretzels, etc.). Based on these score criteria of each questionnaire, this study would assign whether the students are experiencing mental health disorders or substance use problems.

Statistical Analyses Approach

This utilized the Statistical Package for the Social Sciences (SPSS) 25.0 to analyze the data. Demographical information and sex used the Chi-square test to find the relationship between sex and students' population. Independent *t*-tests were used to find out the difference in mental health levels and substance use situation between Chinese domestic college students and Chinese international college students. The binary logistic regression analysis was used to examine the prediction and correlation between substance use issues and mental health problems across two student populations. A two-tailed *p*-value of <0.05 was considered significant for all tests. We used Cox and Snell R^2 and Nagelkerke R^2 to evaluate our model. The larger the value of R^2, the better the model's goodness of fit. Both student groups showed relatively good goodness of fit.

TABLE 1 | Descriptive information of 1,504 college students ($\bar{x} \pm s$).

Characteristics	CSC ($n = 635$)	CSA ($n = 869$)	$\chi 2/t$	p
Gender	1.61 ± 0.49	1.56 ± 0.50	3.9	0.05
Age	19.87 ± 1.48	19.92 ± 1.48	−0.66	0.51
PHQ-9	11.63 ± 5.45	11.41 ± 5.04	0.80	0.42
GAD-7	7.42 ± 5.52	8.87 ± 4.74	−5.46	<0.01**

**Means significant at the 0.01 level (two-tailed).*

RESULTS

Table 1 shows the fundamental demographic characteristics and results of PHQ-9 and GAD-7 of the two student groups. A Chi-square test of independence showed no significant association between sex and student population, $\chi 2_{(1,1,504)} = 3.9$, $p > 0.05$. There was no significant effect of age and PHQ-9 scores ($p > 0.05$) between the students studying in China and America. In contrast, there is a significant difference in GAD-7 mean scores ($t = -5.46$, $p < 0.01$), which indicates that the college students studying in America ($M = 8.87$, $SD = 4.74$) had a high anxiety level than in China ($M = 7.42$, $SD = 5.52$). Although there is no statistical difference for the PHQ-9 scores between the two groups, the number of CSAs ($n = 776$) who experienced depression is more than the number of CSCs ($n = 533$). **Figures 1**, **2** show the specific levels for depression and anxiety based on the score criteria of PHQ-9 and GAD-7. Both groups show a high rate of moderate depression (29.0 vs. 41.6%) and anxiety (35.3 vs. 44.9%). In other words, both student groups were suffering serious mental health problems impacted by the COVID-19 pandemic.

Table 2 provides the comparison between CSC and CSA's frequency of substance use per week by using independent group *t*-test analysis. The results show that CSC had a more severe substance use problem with alcohol (53.7 vs. 56.2%, $p < 0.01$) and drinks (77.6 vs. 61.6%, $p < 0.01$). In contrast, CSAs experienced more serious issues with medicines (41.7 vs. 57.3%, $p < 0.01$), drugs (0.9 vs. 48.3%, $p < 0.01$), and cigarettes (40 vs. 57.4%, $p < 0.01$). In other words, under the influence of the COVID-19 pandemic, both student groups experience the substance use issue, especially for CSAs.

To find the correlation among the substance use frequency, GAD-7, and PHQ-9 scores for the two groups, this study generated a binary logistic regression analysis. The results reveal in **Table 3** that CSCs experiencing depression have a significant association with alcohol [OR = 0.85, 95% confidence interval (CI) = 0.77–0.95, $p < 0.01$] and drinks (OR = 0.89, 95% CI = 0.81–0.97, $p < 0.05$). The probability rates of CSCs with depression problems drinking alcohol and beverages are 0.85 and 0.89 times, respectively, higher than those without depression problems. On the other hand, CSAs experiencing depression

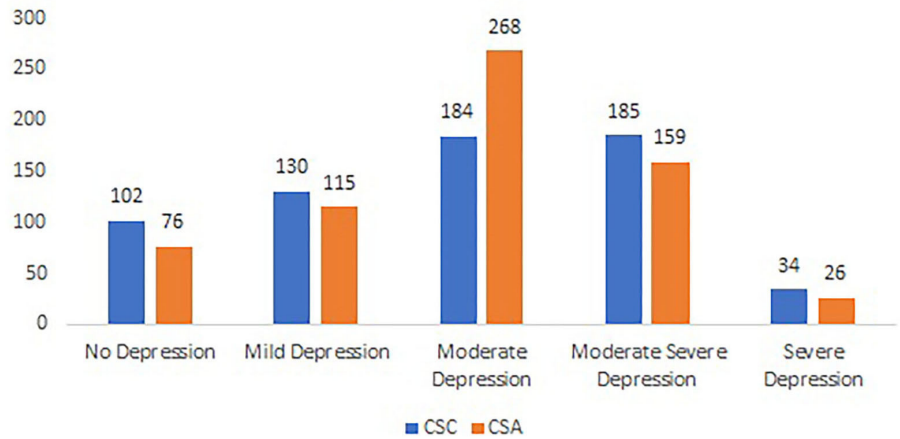

FIGURE 1 | The prevalence of depression between CSC & CSA.

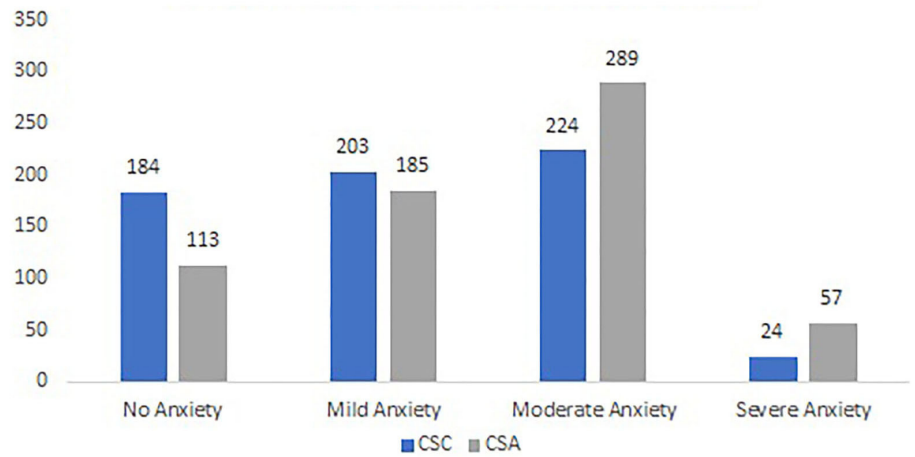

FIGURE 2 | The prevalence of anxiety between CSC & CSA.

have a significant association with drinks (OR = 1.11, 95% CI = 1.04–1.19, $p < 0.01$) and cigarettes (OR = 1.14, 95% CI = 1.06–1.22, $p < 0.01$), indicating that the probability rates of CSAs with depression of drinking beverages and smoke are 1.11 and 1.14 times, respectively, higher than those without depression problems. These students also had a significant association with desserts (OR = 0.90, 95% CI = 0.85–0.95, $p < 0.01$) and drugs (OR = 0.82, 95% CI = 0.71–0.95, $p < 0.05$), which indicates that the probability rates of these students to eat desserts and use drugs are 0.90 and 0.82 times, respectively, higher than those without depression.

Table 4 indicates that the CSA experiencing anxiety problem had a significant association with alcohol (OR = 1.15, 95% CI = 1.04–1.27, $p < 0.05$), drinks (OR = 1.11, 95% CI = 1.04–1.18, $p < 0.01$), and cigarette (OR = 1.16, 95% CI = 1.08–1.24, $p < 0.01$). These students also have a significant association with desserts (OR = 0.90, 95% CI = 0.85–0.96, $p < 0.01$). These results mean that the probability rates of CSAs with anxiety problems of drinking alcohol and beverages, eating desserts, and smoking are 1.15, 1.11, 0.90, and 1.16 times, respectively, higher than students without anxiety problems. However, there is no statistical significance for CSC. The error in the drug variable was caused by the extremum of non-drug takers in students studying in China.

DISCUSSION

This is the first cross-sectional study investigating depression, anxiety, and substance use problems among CSCs and CSAs during the COVID-19 pandemic. There are two significant findings that are consistent with the previous hypothesis. First,

TABLE 2 | Frequency of substance use per week of students who study in China and America (n = 1,504).

	CSC (total n = 635)		CSA (total n = 869)		t	p
	n	%	n	%		
Frequency of substance use per week						
Alcohol					3.77	<0.01**
0 times	294	46.3	381	43.8		
1–3 times	217	34.2	432	49.7		
4–6 times	117	18.4	56	6.4		
>7 times	7	1.1	/	/		
Medicine					−5.42	<0.01**
0 times	370	58.3	371	42.7		
1–3 times	194	30.6	378	43.5		
4–6 times	68	10.7	88	10.1		
>7 times	3	0.5	32	3.7		
Desserts					0.51	0.61
0 times	149	23.5	334	38.4		
1–3 times	358	56.4	404	46.5		
4–6 times	96	15.1	52	6.0		
>7 times	32	5.0	79	9.1		
Drinks					4.44	<0.01**
0 times	142	22.4	334	38.4		
1–3 times	333	52.4	411	47.3		
4–6 times	118	18.6	74	8.5		
>7 times	42	6.6	50	5.8		
Drugs					−16.02	<0.01**
0 times	629	99.1	449	51.7		
1–3 times	1	0.2	384	44.2		
4–6 times	5	0.8	36	4.1		
>7 times	/	/	/	/		
Cigarette					−4.24	<0.01**
0 times	381	60.0	370	42.6		
1–3 times	168	26.5	396	45.6		
4–6 times	72	11.3	48	5.5		
>7 times	14	2.2	55	6.3		

***Means significant at the 0.01 level (two-tailed).*

TABLE 3 | Binary logistic regression analysis for depression disorder for two student population.

	CSC							CSA						
	B	SE	β	p	OR	95% CI		B	SE	β	p	OR	95% CI	
						Lower	Upper						Lower	Upper
Alcohol	−0.16	0.05	8.97	<0.01**	0.85	0.77	0.95	0.10	0.05	3.63	0.06	1.11	1.00	1.23
Medicine	−0.01	0.06	0.02	0.88	0.99	0.87	1.12	−0.07	0.04	3.33	0.07	0.93	0.87	1.01
Dessert	0.04	0.06	0.46	0.50	1.04	0.93	1.16	−0.11	0.03	12.13	<0.01**	0.90	0.85	0.95
Drinks	−0.12	0.05	6.26	<0.05*	0.89	0.81	0.97	0.10	0.03	9.25	<0.01**	1.11	1.04	1.19
Drugs	−0.12	0.22	0.29	0.59	0.89	0.58	1.37	−0.20	0.07	6.97	<0.05*	0.82	0.71	0.95
Cigarette	−0.06	0.06	1.34	0.25	0.94	0.84	1.05	0.13	0.04	12.62	<0.01**	1.14	1.06	1.22

Significant $p < 0.05$ and < 0.01**.*
CI, confidence interval; OR, odds ratio.

TABLE 4 | Binary logistic regression analysis for anxiety disorder for two student population.

	CSC							CSA						
	B	SE	β	*p*	OR	95% CI		B	SE	β	*p*	OR	95% CI	
						Lower	Upper						Lower	Upper
Alcohol	0.01	0.05	0.03	0.87	1.01	0.92	1.11	0.14	0.05	7.31	<0.05*	1.15	1.04	1.27
Medicine	0.03	0.06	0.29	0.59	1.03	0.92	1.15	0.02	0.04	0.26	0.51	1.02	0.95	1.10
Dessert	0.06	0.05	1.34	0.25	1.06	0.96	1.16	−0.10	0.03	11.03	<0.01**	0.90	0.85	0.96
Drinks	−0.06	0.04	2.01	0.16	0.95	0.87	1.02	0.10	0.03	9.79	<0.01**	1.11	1.04	1.18
Drugs	6.15	3,980.35	0.00	1.00	466.91	0.00	/	−0.11	0.07	2.10	0.15	0.90	0.78	1.04
Cigarette	0.06	0.05	1.25	0.26	1.06	0.96	1.17	0.14	0.04	16.44	<0.01**	1.16	1.08	1.24

Significant $p < 0.05$ and < 0.01**.*
CI, confidence interval; OR, odds ratio.

our results indicated that most of our participants were in a depressive and anxious mood, whereas the CSAs had a relatively higher anxiety level. Secondly, both CSCs and CSAs showed problems with the substances: CSCs had a higher tendency to drink alcohol and beverages, and CSAs were more likely to be addicted to medicine, drugs, and cigarettes. Furthermore, these two groups of students with depression problems are more likely to drink beverages.

Both groups of students showed a high prevalence of depression in the study. Compared with the 23.8% prevalence of depression among Chinese college students during the non-COVID-19 period (10), the depression rate (35.4%) of Chinese college students during the COVID-19 pandemic appeared higher, which is consistent with the previous study (8, 9, 30). Despite the difference in the number of participants for the two studies, these results indicated the elevated risk of depression in Chinese college students during the pandemic. Both student groups struggled with many issues and experienced high depression and anxiety levels influenced by the COVID-19 pandemic; however, CSAs faced more severe problems. Of course, there are some pre-differences that can potentially contribute to the differences we identified. For example, the drive for higher education is different between Chinese and American college students. CSAs may tend more to consider higher education abroad as a life-changer, as they believe that studying abroad would enable them to understand the differentiation of personal development and contribute to their improvement (31) and thus might cause them to experience more severe emotional symptoms.

Many American universities were forced to close suddenly and changed the learning model from in-person to remote, which led to discontinuing their studies, research projects, and internships. As a result, their stress level increased to a peak with various stressors (5, 12). The social life of these students has also been harmfully influenced, as they have to be separated from their friends, classmates, and professors for an extended period, which increases their loneness. The feelings of social isolation are on the rise, as they believe they may not see their friends anymore, and some cannot even say goodbye to each other (32, 33). Besides, discrimination against the Chinese during the COVID-19 pandemic may also lead to a higher level of anxiety. The news against China and Asia across the world stemmed repeatedly. For example, one of the most notable anti-Asian COVID-19 discrimination was spoken by the former President of the United States, referring to the virus as the "China virus" (15–17). As a result, the Chinese international college students were under severe negative bias and lived in fear of being discriminated against, which significantly influenced their mood and self-esteem. Furthermore, going back to China caused the time differences issue, where these students have to stay up late to take classes remotely, leading to poor physical health (9, 34). These "multiple jeopardies" overwhelmed these students and made their anxiety and stress levels rapidly rise.

Our results also showed that both student groups have substance use problems. CSCs were facing more severe alcohol and beverage issues, as the minimum age for buying alcohol is 18 years in China, so Chinese college students are more accessible to get it than students in America (16, 35). Besides, alcohol use in moderation is considered good for the health in China. Therefore, it is difficult for these Chinese college students to manage the capacity for liquor. With immature minds and scanty experiences of life, they would easily be drinking alcohol excessively when others urge them to drink at a party or social event (36). Loneliness could also lead these Chinese college students to overly drink alcohol, so they frequently use alcohol to ease their pain and alleviate their negative feelings (37–41). Other studies also indicated that loneliness was more common among people, such as healthcare workers, exposed to COVID-19, stressing the role of potential to counteract the adverse effects of higher levels of loneliness (39–41). Coffee is one of the most popular drinks among college students (42), particularly for students who have had insufficient sleep. They need energy and keep sober to reduce fatigue to listen to the class and prepare for the exams during the daytime (24, 43). Thus, these college students seek caffeine from coffee to increase energy and improve their study performance, as caffeine is the most frequently consumed central nervous system stimulant in the world (44, 45).

CSAs were experiencing more severe problems in medicines, drugs, and cigarettes. The number of CSAs may be impacted subtly by the western culture with higher drinking and smoking habits (20, 22). One of the examples of medicines in our survey is dietary supplements. The students who live on the American campus may be influenced imperceptibly by the American lifestyle and eating habits of eating dietary supplements to make a healthy and strong body (46). During the COVID-19 pandemic, taking dietary supplements every day would be effective, as everyone believes that they would be protected from the virus if they have a healthy body (47). There are several psychological and physical benefits of taking these dietary supplements: obtaining adequate amounts of nutrients and maintaining their health, losing weight, preventing diseases, and improving immunity (48–50). Furthermore, sleeping pills such as melatonin are also examples in our medicine category. College students are usually associated with sleep difficulties and insufficient sleep, where they are constantly forced to stay up late by the academic stress and assignment workload (51–53). Meanwhile, after these CSAs returned to China, they needed to stay up late to take the remote class. Therefore, these students' sleep patterns and biological clock have been disturbed. Their physical and psychological health collapsed under the pressure of stress from academic life, social activities, and internship, and this explains why they would frequently use sleep medicines to have a good sleep or immediately fall asleep.

Prior research concluded that college students are one of the groups easy to be addicted to smoking (54). Electronic cigarettes (E-cigarette) have increased in popularity among college students and have become the most common tobacco product among this generation (55). During the COVID-19 pandemic, these college students were suffering from the pressure from academic, social, and daily routines. Compared with cigarettes, the E-cigarette is a "healthy product" that could make them quit/reduce tobacco use and release stress (56, 57). Many studies have revealed that youths who use tobacco products (including e-cigarettes) tend to use cannabis than non-tobacco users (58, 59). Similar problems happen with drugs. Late adolescence and young adulthood, the college-age period, are peak developmental periods for drug involvement. Non-medical use of prescription medications is one of the common phenomena, including analgesics and analeptics, in Chinese college students (22, 60). The students who take drugs might believe that the drugs could help them get rid of low emotions and avoid annoyance easily. Another benefit of the drugs could be to medicate sleep problems. The students reported that sleep onset is more rapid after marijuana use (61, 62).

The present study also confirmed a known association between substance use and affective symptoms (depression and anxiety) in both student groups. The social mechanism might be one of the explanations. As the school and government policies established, most of the students needed to study at home. Under tremendous stress from academics, parents, and graduation, the inside feelings of loneliness and frustration of these students were exaggerated (63). A previous study found that binge eating and drinking could be one of the symptoms caused by loneliness (64), which results in loneliness being the possible reason causing these college students to use substances frequently. In addition to the substance use problem, loneliness also caused adverse effects on students' mental health, such as strong associations with suicide ideation and attempts (65) and depressive mood (63). The student population has severe mental health problems and frequent substance use issues that might be attributed to extreme loneliness.

In conclusion, the mental health and substance use problem of the Chinese student population study in China and America affected by the epidemic differs significantly, especially for CSAs. It is imperative to vigorously develop mental health services in China and promote mental health for these college students more deeply and broadly. The effective method is examining the problems in a group or sample of college students and finding out the problems, then taking measures to deal with each problem that these college students have. We recommend that professors, counselors, and administrative staff working in colleges facilitate taking necessary steps to help these students, including self-help brochures, psychoeducational studies, and individual and group counseling. Thus, these people who work in colleges should proactively reach out to all student populations, identify students who need help or are at high risk of mental health problems, and plan tailored treatment to counteract the adverse psychological effects. In addition, future tailored prevention intervention programs and more discussion are needed in China about the regulation of substances that may be beneficial to reduce the risk of substance use among Chinese college students. After the series mentioned earlier are implemented, the risk of students being infected can be reduced, at the same time, lower mental health problems. Even relevant health departments could establish a reasonable system that can be extended to decline the risk of future public health emergencies.

This study has several limitations that should be improved in future studies. First, its sample size was relatively small, and our sample is not fully representative of the general college student population in China. Second, we should ask what exact substance they are using so frequently. Take medicines as an example. What is the frequency of use of specific medication that participants are using? We do not know the frequency of use where participants answered benzodiazepines and/or selective serotonin reuptake inhibitors. Previous studies have revealed the past or current treatment, as psychotherapy and pharmacotherapy may have a significant impact on the clinical outcome explored in this study (substance use and affective symptoms): cognitive-behavioral therapy can be used to modify maladaptive automatic negative emotions of individuals about the pandemic (66); although benzodiazepines and selective serotonin reuptake inhibitor are known as the standard treatment of anxiety and insomnia, it is still a drug that may produce alterations in mood, cognitive, and psychomotor functions (67); the increase in benzodiazepines during the pandemic may be considered a proxy for increased anxiety that influences mood problems (68). The future study needs to examine the high-risk population with a current or history of pharmacotherapy and psychotherapy. There is a reason to suspect that social desirability could cause individuals to report inaccurate levels of participation in each of the mentioned behaviors, and the data here failed to capture this possibility. The last limitation is that we

do not continue to track the emotional and substance problems of these CSAs after returning to the college campus. Further prospective cohort studies are needed to explore how Chinese college students' differences in mental health and substance use change under the COVID-19 influence more specifically to track the emotional and substance problems of CSAs back to college life and add items related to psychotherapy and pharmacotherapy to find more clinical implications. The future study could also find more social and biological mechanisms among these Chinese college students correlated to their mental health and substance use problems change.

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 Zhejiang Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML and CQ designed the study, managed the literature review, and drafted the report. ML, YW, and WS collected the data. ML and WS undertook statistical analyses and took the lead in writing the manuscript and approved the final manuscript. CQ commented on the manuscript. All authors contributed to the article and approved the submitted version.

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