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Broadening the scope of addiction medicine: Integrating co-morbid conditions, polysubstance use, and patient experiences into substance use treatment

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Broadening the scope of addiction medicine: Integrating co-morbid conditions, polysubstance use, and patient experiences into substance use treatment

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Editorial: Broadening the scope of addiction medicine: Integrating co-morbid conditions, polysubstance use, and patient experiences into substance use treatment

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KEYWORDS

substance use disorder (SUD), substance use treatment, opioid use disorder (OUD), opioid treatment, addiction medicine, polysubstance use, integrated care approach

Editorial on the Research Topic
Broadening the scope of addiction medicine: Integrating co-morbid conditions, polysubstance use, and patient experiences into substance use treatment

Introduction

Addiction medicine is often siloed into treatment for a primary drug. However, low rates of treatment retention and success simultaneously occurring with increased rates of substance use disorders (SUDs), have led to calls to re-evaluate what it means to treat addiction. Importantly, there is a greater understanding that addiction exists in a feedback loop consisting of multiple factors such as social determinants of health, polysubstance use, and co-morbid mental and physical conditions. In addition, addiction medicine often confronts individual, organizational and structural barriers that prevent it from addressing these co-occurring issues, despite the fact they can directly impact treatment outcomes. The purpose of this issue was to highlight areas that can impact the development and treatment of substance use disorders, as well as ways that addiction medicine can be broadened by the development and implementation of integrated care, with the end goal of treating the whole person rather than a narrowed addiction, thus improving treatment outcomes for those who need it most.

Polysubstance use and co-morbid conditions

Polysubstance use is a growing concern, including among people who use opioids, youth and young adults, and individuals with co-morbid conditions. Addressing these underlying issues, as well as identifying motivations to reduce substance use is paramount in meeting the goals of treatment for SUD. Co-morbid psychological or mental health problems are of special concern. One such example is borderline intellectual function (BIF), described by Hetland et al. The authors investigated the prevalence of BIF in Norway among individuals with poly-SUD. Results indicate that the number of patients with BIF is significant and it is associated with increased psychological distress among individuals engaged in poly-SUD treatment.

Several manuscripts in this issue note that identifying and treating underlying mental health co-morbidities can improve SUD treatment outcomes. First, findings from Gerhardt et al. show that among German patients in treatment for SUD, mental distress symptoms resulting from histories of childhood maltreatment (e.g., anxiety, depression, perceived stress) are associated with craving during treatment. Second, among rural government-financed health insurance beneficiaries in the United States (i.e., Medicare/Medicaid) who receive care at an opioid use disorder (OUD) treatment program, co-morbid anxiety, depression, and PTSD are common, as are stimulant and sedative use disorders (Lister et al.). And finally, utilizing a large-scale survey of American college students, Striley et al. examined the relationship between the use of vaping products and non-suicidal self-injury (NSSI). Findings documented a relationship between vaping, NSSI, suicidal ideation, and other substance use.

Together, these manuscripts highlight the need for additional screening and assessment of cognitive impediments, of which BIF is but one example, among individuals entering treatment for SUDs. Understanding the existence and severity of such impediments would allow treatment providers and clinicians to account for more tailored care management, as well as potential impacts (e.g., psychological distress) on treatment outcomes (Hetland et al.). Moreover, more comprehensive screening and assessment would likely indicate therapeutic targets for individuals with childhood maltreatment (Gerhardt et al.) and identify individuals who require additional support or integrated mental health care (Lister et al.; Striley et al.). Indeed, the recognition of the need to screen for co-morbid mental health and substance use disorders was the basis of the work of Shahzad et al. who translated and adapted the Cognitive Emotion Regulation Questionnaire into Urdu and tested it among a sample of Pakistani patients in treatment for SUD.

Understanding patient motivations is also critical for enhancing addiction medicine. As documented by Fortin et al., the desire to reduce one's consumption of illegal cannabis is a primary motivation for the use of cannabidiol products (CBD), especially among individuals who co-use alcohol and tobacco. CBD consumption was also found to reduce cannabis withdrawal symptoms.

Patient experiences and integrated care

A key motive for this special issue on broadening the scope of addiction medicine was to highlight the urgent need for integrated care. Persons with SUDs suffer from a range of comorbid conditions and engage in a number of risk-laden behaviors that require treatment of the whole person in order to achieve desired treatment outcomes.

Several of the articles report on patient perspectives as a call to action to manage the multifaceted needs of persons with SUDs. Stoltman et al. report data from a medication for OUD (MOUD) clinic in West Virginia, noting that, outside of pregnant women, reproductive and sexual health (RSH) services are significantly lacking in OUD populations. While knowledge and uptake of contraceptives in both men and women was low, 40% indicated an interest in RSH services co-located with their MOUD clinic such as contraceptive counseling and provision, STI testing, and sexual dysfunction management. Stoltman et al. reinforce the benefit of co-location in rural areas, where it can be challenging to access multiple points of care.

Surratt et al. also report on patient perceptions of sexual health services in rural areas, specifically the barriers to initiating pre-exposure prophylaxis (PrEP) as a form of HIV prevention among persons who inject drugs (PWID) in southeastern Kentucky. HIV continues to disproportionately affect PWID, particularly in rural areas that experience distinct barriers. Individually, there were moderate perceptions of HIV risk, low awareness and knowledge of PrEP, and uncertainty about PrEP resulting from stigma from law enforcement and healthcare personnel, where concerns of privacy deterred PrEP-seeking behaviors. Layered on are structural barriers existing in the form of "PrEP deserts" where few to no qualified providers exist. Integrating PrEP services and education with existing syringe service programs would mitigate many barriers unique to PrEP-seeking in isolated rural areas.

While Stoltman et al. and Surratt et al. elucidated patient perceptions to highlight the benefits of integrated care, several articles reported data from programs that have implemented such care practices. Losikoff et al. note that cases of hepatitis C (HCV) have drastically increased in the United States. However, treatment initiation for HCV among PWID is low, at <10% among those screened.

This may be due, in part, to a fear of stigma from healthcare professionals. As such, Losikoff et al. report on an outpatient OUD treatment center providing MOUD that developed a system to co-locate HCV services with MOUD, including screening, provider education, patient education, and treatment. Such integrated care led to HCV cure rates comparable to people who do not use drugs, lower rates of other substance use, and greater utilization and retention of OUD treatment.

Nolan et al. report on a bridge-to-health program in a Midwest academic hospital, developed for treating PWID that present with infections associated with injection drug use (IDU). To improve post-discharge outcomes related to both IDU and OUD, a multidisciplinary team provided patients receiving MOUD with infection-related care, harm reduction education and take-home kits, and follow-up care 90 days post-discharge, ending with a handoff to a community provider for continued addiction care. Qualitative interviews indicated that participants found the program beneficial for managing acute pain-related issues and improving access to MOUD, had positive perceptions of the multidisciplinary team, yet also noted issues surrounding hospital confinement and stigma from healthcare personnel, issues of important consideration in the implementation of integrated care.

Finally, Martin et al. raise the issue of poor sleep quality, a comorbidity of growing concern in SUD research and care. There may exist a bi-directional relationship between SUDs and sleep, wherein one may negatively impact the other. As part of a broader study seeking to classify individuals with SUD along neurofunctional domains, individuals with SUDs were compared to people who do not use drugs across sleep quality. Martin et al. report that poor sleep was more prevalent compared to controls in both men andwomen, and these findings were most robust for those with OUD or cannabis use disorder. The data also suggest that there are sex-specific factors, with poor sleep quality more prevalent among women, which may suggest that sleep dysfunction in individuals with SUDs may need to be addressed in sex or gender-specific ways.

Future directions

Although examining different substance use populations and themes, the manuscripts in this issue highlight new areas of addiction medicine research and offer guidance for future directions. Specifically, the development of screening and assessment tools for treatment-seeking people who use drugs is critical, including translating existing tools into new languages. Such work allows for the integration of care to diagnose, treat, and prevent co-morbid mental health problems, and infectious diseases and address sleep quality and additional healthcare needs. Recognizing that addiction medicine needs to be more broadly defined, and addressing the barriers that exist in order to implement integrated or multidisciplinary care, are urgently needed in order to improve treatment outcomes and mitigate the substance use crisis that exists in the world today.

Author contributions

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

Conflict of interest

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

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ORIGINAL RESEARCH
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Prevalence and Characteristics of Borderline Intellectual Functioning in a Cohort of Patients With Polysubstance Use Disorder

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Objective: To determine the prevalence and associated demographic and clinical features of borderline intellectual functioning (BIF) among individuals with polysubstance use disorder (pSUD).

Methods: We applied a cross-sectional analytical design to data from the Norwegian STAYER study (n = 162), a cohort study of patients with a pSUD from the Stavanger University hospital catchment area. We used Wechsler Abbreviated Scale of Intelligence Full Scale IQ (FSIQ) to define BIF (FSIQ = 70–85) and non-BIF (FSIQ = >85) and collected demographic and clinical data using semi-structured interviews and self-reports on the Symptom Checklist 90-Revised (SCL-90-R) and the Satisfaction With Life Scale (SWLS).

Results: The prevalence of BIF was 18% in the present study. The presence of BIF was associated with higher SCL-90-R GSI scores than in the non-BIF group. There were no significant differences between the BIF and non-BIF groups regarding age, gender, participation in meaningful daily activity, years of work experience, years of education, satisfaction with life, level of care, treatment attempts, age at substance-use onset, years of substance use, history of injecting drugs, or age of onset of injecting drugs.

Conclusion: The present study confirmed a higher prevalence of BIF among patients with pSUD than expected from the distribution of IQ scores in a general population. Elevated SCL-90-R GSI scores suggested that BIF is associated with increased psychological distress in patients receiving treatment for pSUD. Further studies on this association, and its effect on treatment procedure and outcomes are strongly warranted.

Keywords: polysubstance use disorder, borderline intellectual functioning, symptom check list-90-R, satisfaction with life scale, intelligence quotient, prevalence, substance use disorder

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INTRODUCTION

Intellectual functioning in patients with substance use and abuse has received increased attention during the last decade (1, 2). This follows the fact that intellectual functioning (e.g., reasoning, planning, problem solving, judgement, and abstract thinking) is a core predictor of a variety of life outcomes, with the most severe impairments observed in patients with an intelligence quotient

(IQ) two standard deviations below the population mean (IQ < 70) (3–5). In the present study, we focused on the impact of borderline intellectual functioning (BIF), which is defined as an intelligence quotient ranging between one and two standard deviations below the population mean (IQ = 70–85). Based on previous studies, we know that adults with BIF have an increased vulnerability for developing psychiatric disorders, including a substance use disorder (SUD) (2, 6–12). Assessment of intellectual function should therefore be considered an important component of clinical examination and treatment planning of SUDs.

According to the normal distribution of IQ scores (Bell Curve), approximately 13.6% of individuals in the general population would be allocated to a subgroup defined with BIF, with elevated rates commonly observed in clinical populations (13). Nevertheless, the frequency estimates within clinical groups are uncertain because of methodological differences between studies (ascertainment biases, the choice of diagnostic tools, service configurations, and entry criteria). In addition, there is a historical lack of terminological consensus and classification of BIF (14, 15) and non-agreed-upon diagnostic criteria in diagnostic manuals like the DSM-V and ICD-10 (16, 17). Nevertheless, studies have shown that individuals with BIF exhibit difficulties in several aspects of life, that these difficulties may occur at a similar level as for individuals with a diagnoses of intellectual disability (ID), and that individuals with BIF may need targeted support (1, 4, 6, 9, 10, 14, 18–21).

Individuals with BIF may not only be severely impaired; they are also less likely to receive adequate treatment for mental health issues, less likely to receive psychotherapy, and more likely to be treated with psychotropic medication than individuals with mental health problems in the general population (10, 22). This is obviously the case in individuals with co-occurring BIF and SUD; they tend to show adverse rehabilitation outcomes when offered mainstream SUD treatment, because of factors such as reduced disposition to change and desire for help (23, 24), lower treatment compliance (25), high drop-out rate (26–28), relapse during treatment (29), and negative treatment experiences (30). Therefore, it is alarming to realize that impaired intellectual functioning is often overlooked in treatment programs for patients with SUD, even though it can be a key clinical factor in predicting treatment needs and prognosis (24, 29, 31–34).

There is a dearth of research on BIF in general, and BIF in SUD populations in particular. When included in studies, BIF is typically classified broadly as mild-to-borderline intellectual disability (MBID) with IQ ranging between 50 and 85, or treated as a control group (4). The major thrust of research on the co-occurrence of BIF and SUD originate from the field of ID services and target substance use in individuals with a known ID diagnosis. Subsequently, findings are mainly published in journals in that field, rather than in journals in the field of medical addiction (2). Initiatives to develop a framework around the clinical and adaptive needs of patients with co-occurring SUD and BIF have been sporadic and uncoordinated (14).

Studies examining the prevalence rates of BIF in SUD populations are scarce, and their prevalence rates vary considerably. Braatveit et al. found the prevalence rate of BIF among patients with SUD to be 23% (29), and Luteijn et al. reported a MBID prevalence rate of 39% (24). At the other end of the scale, VanDerNagel et al. reported a prevalence estimate as low as 3% (35). Furthermore, prevalence data for BIF and MBID are difficult to compare because of lack of consensus on terminology, differences in group characteristics, levels of disability, treatment settings, comorbid psychiatric disorders, and definition and scope of substance use (2, 13, 36). Taken together, studies of BIF based on standard instruments in well-characterized cohorts of patients with SUD are obviously warranted.

The lack of epidemiological data and findings showing that BIF may be vital for the broader understanding and treatment of patients with SUD motivated the present study to investigate the prevalence and characteristics of patients with BIF in a typical group of individuals receiving treatment for polysubstance use disorder (pSUD). Polysubstance use is common in both clinical, and population samples (37, 38). Moreover, polysubstance use patterns is frequent in patients seeking treatment for mono-substance disorders (39–43). In this context, pSUD refers to the use of multiple substances as part of a pattern of problematic substance use, in which the patient meets criteria for SUD for some, but not necessarily all substances used (44). Compared with mono-substance users, polysubstance users have an earlier onset of substance use (45), are younger (37), have higher levels of psychological distress and personality disorders (45–50), more persistent cognitive impairments (51), and poorer social adjustment (37, 46, 48, 52). Studies suggest that these characteristics are associated with increased risk of dropout and relapse (27, 53–57). Thus, patients with pSUD may have a more severe clinical profile than patients with mono-substance use and consequently pose a challenge for SUD-treatment services and the mental health care system (46, 53, 58, 59).

The aim of the present study is twofold: (1) to provide a prevalence estimate of BIF in patients with pSUD receiving mainstream SUD treatment (2) to investigate clinical and demographic features in subgroups of patients with and without co-existing BIF.

MATERIALS AND METHODS

Study Design and Patient Characteristics

The study used data from the Stavanger Study of Trajectories of Addiction (STAYER), an ongoing, prospective, longitudinal cohort study of the neurocognitive, psychological and social recovery in patients with polysubstance use who started a new treatment sequence in the Stavanger University Hospital catchment area (60, 61). See Andersson et al. (54) for more details regarding the structure of Norwegian SUD-treatment. To be eligible for specialized treatment for SUDs within the Norwegian public health service, patients must meet the criteria for a F1x.1 (harmful use) or F1x.2 (dependency syndrome) diagnosis, as defined by the ICD-10 (17). We performed baseline assessment after 2 weeks of abstinence, in an attempt to minimize contamination from drug withdrawal and the acute neurotoxic effects from psychoactive substances (62). Trained research personnel of the STAYER research group collected all data. In the

present study, polysubstance users were defined as patients with SUD who reported the use of multiple substances within the last year before inclusion. The project was approved by the Regional Ethics Committee (REK 2011/1877) and conducted according to its guidelines and those of the Helsinki Declaration (1975). All participants provided signed informed consent.

Participants

A total of 208 patients were recruited consecutively at convenience from 10 outpatient and residential treatment facilities within the Stavanger University Hospital catchment area between March 2012 and January 2016. All patients had been voluntary admitted for SUD-treatment.

Patients were included if they (1) signed a written informed consent, (2) were enrolled in a new rehabilitation sequence by the substance use treatment service, (3) reported use of multiple substances within the last year before inclusion, and (4) were 16 years or above. Patients received a compensation of NOK 400 for their time at the baseline testing. Of the 208 patients in the STAYER cohort, 44 patients were excluded from the present study because of mono-substance use (alcohol $N = 35$, cannabis $N = 1$) or lack of substance-related disorders (e.g., gambling $N = 8$). We excluded one case because of missing IQ scores and one case because of an IQ score <70; thus, the remaining sample of patients with pSUD comprised 162 individuals.

Assessment

We obtained demographic, neurocognitive, psychological, and social-functioning data using semi-structured interviews, cognitive tests, and self-reported measures at the baseline assessment. We used a preliminary version of the National Quality Register for Substance Abuse (KVARUS) (63), a semi-structured interview to obtain information on the type of substance intake, initial age at use, treatment and work history, and educational, vocational, and social adjustment.

Wechsler Abbreviated Scale of Intelligence

Wechsler Abbreviated Scale of Intelligence (WASI) (64) was used to assess intellectual function. WASI was created to establish a brief and reliable estimate of intellectual functioning and comprises four subtests, i.e., two verbal measures of crystalized intelligence (Vocabulary and Similarities), which yield a verbal intelligence quotient (VIQ), and two non-verbal tests of fluent intelligence (Block Design and Matrix Reasoning), which yield a performance intelligence quotient (PIQ). BIF was defined as a WASI Full-scale IQ (FSIQ) ranging between 70 and 85, and non-BIF was defined as a FSIQ > 85.

Satisfaction With Life Scale

Satisfaction with life was assessed using the Satisfaction With Life Scale (SWLS) (65). SWLS is a self-report questionnaire comprising five items to measure the respondent's global life satisfaction with a seven-point Likert-type format (ranging from 1-strongly disagree to 7-strongly agree). SWLS has demonstrated excellent psychometric characteristics (66) and also validated for individuals with ID (Cronbach's alpha = 0.79) (67). A score of 20 represents a neutral point on the scale; scores between 5 and 9 indicate dissatisfaction with life, while scores ranging between 31 and 35 indicate that the respondent is very satisfied with life (66).

Symptom Checklist 90-Revised

We used the Symptom Checklist 90-Revised (SCL-90-R), which is a 90-item self-report measure (68) assessing psychological symptoms and distress. SCL-90-R is widely used in clinical practice and research, and validated for patients with SUD and individuals with ID (68–70). Items are rated on a five-point Likert scale indicating the degree of distress, ranging from 0 (not at all) to 4 (severely) during the 7 previous days. The checklist comprises nine symptom dimension subscales: Somatization, Obsessive–Compulsive Disorder, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism, in addition to a global severity index (GSI), which was used here as a measure of psychological distress.

Statistics

The statistical software package SPSS version 26 (IBM Corp., released 2016) was used for all statistical analyses. Statistical significance was set at $P < 0.05$, and assumptions of normality evaluated based on Q–Q plots and by inspecting the residuals. A frequency analysis was run for the BIF and non-BIF groups. Independent-sample *t*-tests were performed to evaluate differences between-group means, and the chi-squared test of independence was used in case of categorical variables.

Because of an association between BIF status and SCL-90-R GSI score, we performed additional *post hoc* analyses to explore this association. As a result of the modest size of the BIF group, we opted not to use BIF status as a dependent variable in logistic regression analyses because of the risk of overfitting the regression model (71). Instead, we performed a multiple regression analysis (forward selection) with SCL-90-R GSI score as the dependent variable and BIF status, age, gender, years of education, age of onset of substance use, history of injecting drugs, and SWLS sum score as independent variables.

RESULTS

Among the 162 participants included in the analyses, 29 (17.9%) were classified as having BIF. **Table 1** shows the demographic and clinical features in the total sample and stratified according to intellectual functioning (i.e., the BIF and non-BIF group). Participants in the BIF group (M = 1.4, SD = 0.8) exhibited significantly higher SCL-90-R GSI scores than the non- BIF group [M = 1.1, SD = 0.6; $t_{(160)} = 2.5$, $p < 0.05$], indicating a higher degree of self-reported psychological distress in the former group. No further significant differences were detected between the BIF and non-BIF groups on any demographic or clinical feature.

Figure 1 shows that the distribution of IQ scores in the present cohort was comparable to the expected distribution in the general population, with a small shift toward the lower end of the scale.

Table 2 lists the WASI scores in the total sample and within the two groups. The mean WASI FSIQ in this BIF group was 80.3

TABLE 1 | Demographic and clinical features of the present sample stratified according to intellectual functioning.

	Total sample		BIF ($n = 29$)		Non-BIF ($n = 133$)		Statistics		
	n	Mean (SD)/*n* (%)	*n*	Mean (SD)	*n*	Mean (SD)	*t*(df)/Value (df)	Cohen's d	*P*-value
Age	162	27.6 (7.5)	29	26.1 (8.4)	133	27.9 (7.3)	−1.22 (160)	0.24	0.225
Male gender*	162	106 (65.4)	18 (62.1)		88 (66.2)		−0.18 (1)		0.674
Income from work or other meaningful daily activity*	162	101 (62.3)	17 (58.6)		84 (63.2)		0.21 (1)		0.648
Years of work experience	146[a]	5.6 (5.8)	26	4.0 (4.1)	120	5.9 (6.1)	−1.51 (144)	0.36	0.134
Education, years	162	11.6 (1.7)	29	11.2 (1.7)	133	11.7 (1.7)	−1.18 (160)	0.24	0.239
Treatment attempts	162	1.6 (2.4)	29	1.5 (2.0)	133	1.6 (2.4)	−0.29 (160)	0.06	0.776
In-patient*	161[a]	95 (58.6)	20 (71.4)		75 (56.4)		2.16 (1)		0.141
SCL-90-R GSI	162	1.1 (0.7)	29	1.42 (0.8)	133	1.1 (0.6)	2.48 (160)	0.46	0.014
SWLS sum score	162	15.4 (6.3)	29	14.8 (6.1)	133	15.5 (6.4)	−0.57 (160)	0.12	0.569
Age of drug debut	160[a]	13.1 (2.1)	29	12.7 (1.7)	131	13.1 (2.2)	−0.95 (158)	0.21	0.343
Years of drug use	160[a]	14.5 (7.5)	29	13.3 (8.1)	131	14.8 (7.4)	−0.95 (158)	0.18	0.343
Injected drugs*	161[a]	98 (60.5)	15 (51.7)		83 (62.9)		1.24 (1)		0.265
Age at first use of injected drugs	98[b]	19.7 (5.0)	15	18.2 (5.8)	83	20.0 (4.8)	−1.29 (96)	0.36	0.202

*Chi-squared test of independence.
[a]Numbers lower than 162 are caused by missing data.
[b]Participants with a history of injecting drugs.

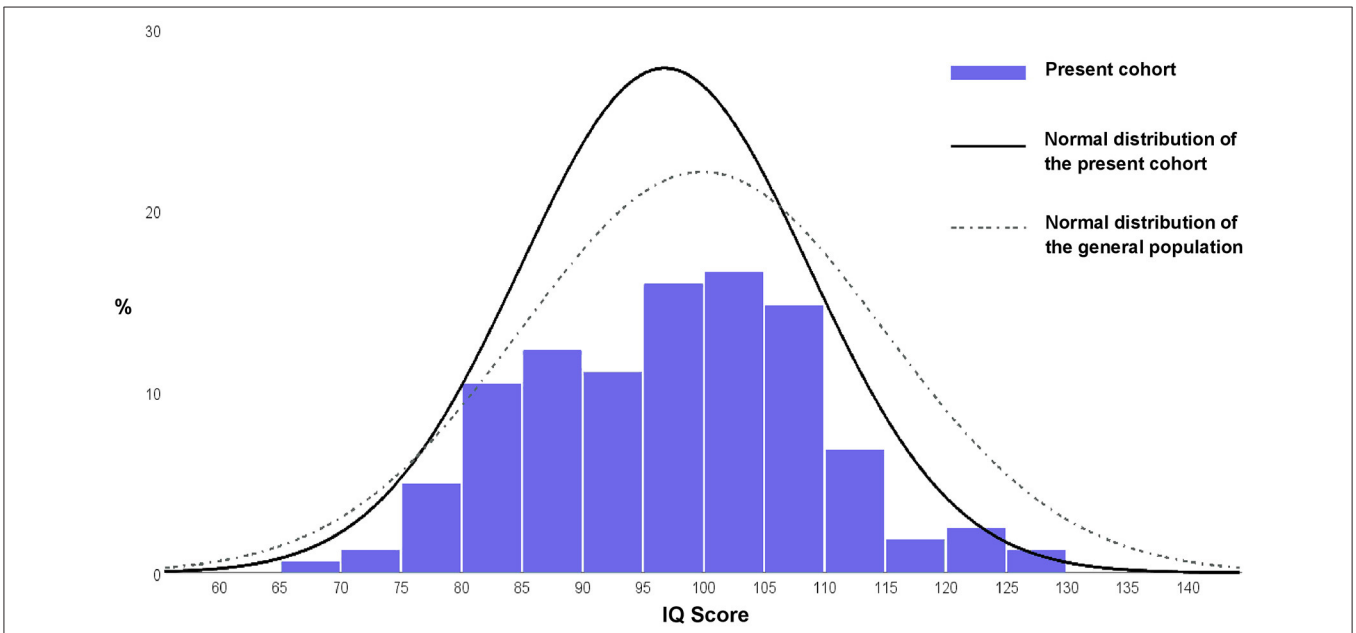

FIGURE 1 | Histogram of the distribution of IQ scores in the present cohort compared with the theoretical distribution of the general population. One participant with IQ < 70 was included in the histogram.

(SD = 3.8, 95% CI = 78.8–81.7), whereas the mean WASI FSIQ was 100.8 (SD = 9.4, 95% CI = 99.1–102.4) in the non-BIF group.

A multiple regression analysis using the SPSS' forward selection algorithm was computed to further investigate the association between the presence of BIF and the SCL-90-R GSI scores. The SCL-90-R GSI scores were included as the dependent variable and the BIF status as well as age, gender, years of education, age of onset of substance use, history of injecting drugs, and SWLS sum score as independent variables. This procedure yielded a significant regression equation $F_{(3,156)} = 14.882$, $P < 0.001$; $R^2 = 0.223$), leaving BIF status as well as age, and SWLS sum score as significant predictors of the SCL-90-R GSI scores (see **Table 3** for details).

DISCUSSION

The prevalence rate of BIF in patients with polysubstance use was 18% in the present study. There were few statistically significant

TABLE 2 | WASI scores in the total sample stratified according to intellectual functioning.

	Total sample		BIF ($n = 29$)		Non-BIF ($n = 133$)		Statistics		
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*t*(df)	d	*P* value
WASI FSIQ	162	97.1 (11.7)	29	80.3 (3.8)	133	100.8 (9.4)	−11.5 (160)	2.85	<0.001
WASI VIQ	162	95.1 (12.7)	29	82.5 (8.2)	133	97.8 (11.8)	−6.6 (160)	1.51	<0.001
WASI PIQ	162	99.9 (13.2)	29	82.0 (8.1)	133	103.8 (10.7)	−10.4 (160)	2.30	<0.001

TABLE 3 | Summary of the regression analysis with SCL-90-R GSI as dependent and BIF status, age, and SWLS sum as independent variables.

Variable	B	95% CI	β	*t*	*p*
(Constant)	2.533	[2.082, 2.983]		11.106	<0.001
SWLS Sum score	−0.039	[−0.054, −0.024]	−0.369	−5.219	<0.001
Age	−0.021	[−0.033, −0.008]	−0.233	−3.283	0.001
BIF-status	−0.256	[−0.499, −0.014]	−0.148	−2.086	0.039

BIF status is coded as 0 for BIF and as 1 for non-BIF.
CI, confidence interval for B.

differences between the BIF and non-BIF groups regarding demographic and clinical features. However, patients with BIF had significantly elevated SCL-90-R GSI scores, indicating a higher degree of psychological distress compared with the non-BIF group. A regression analysis confirmed the importance of BIF status, even when controlling for a range of demographic and clinical data.

The prevalence rate of BIF found in the current study was higher than that observed in the general population, but still somewhat lower than reported by some previous studies of patients selected from in-patient SUD populations (24, 29). However, the sample included in the study of Luteijn et al. (24) was selected from a forensic unit and gauged the prevalence rate of MBID, not BIF. Although it may be tempting to hypothesize that patients receiving in-patient treatment have more impaired intellectual functioning compared to patients receiving out-patient treatment, the results of the current study do not support this notion, as there were no significant differences in the prevalence rate of BIF between these two groups. The prevalence rate of BIF found in the present study was indeed higher than the 3% identified by VanDerNagel et al. (35). However, those authors relied on the identification of individuals with BIF through a review of caseloads and patient records. Because of the low recognition of MBID/BIF, those findings are expected to provide underestimations compared with the results of studies including direct assessment of intellectual functioning.

The regression model indicated independent negative associations between the independent variables SWLS sum score, age, and BIF-status and SCL-90-R GSI score among patients with pSUD. The association between SWLS sum score and SCL-90-R GSI score was expected, given the conceptual similarities between psychological well-being and life satisfaction in human functioning. In addition, age was negatively associated with SCL-90-R GSI scores, a finding that was expected based on previous studies (44, 72). A strong association between BIF and an elevated SCL-90-R GSI score among patients suffering from pSUD is a main finding of the present study. This finding is in accordance with previous studies reporting associations between psychological distress and impaired intellectual functioning (19, 73–76). Although causality of the association between SCL-90-R GSI score and BIF status in the present study is unknown, several direct and indirect paths may be suggested.

Individuals with impaired intellectual functioning may be susceptible to the development of psychological ill-health and impaired social adjustment due to reduced capacity for problem-solving, flexible adjustment and stress tolerance (77). Conversely, psychiatric disorders may induce temporary state-specific neurocognitive disruptions impairing cognitive performance (78–80). Finally, the selected measures may not reflect disparities in latent cognitive abilities as psychological distress may impede test performance indirectly through lack of performance motivation, low self-efficacy and increased engagement in distracting worrisome thoughts or task-irrelevant cognition.

The use of an IQ criterion in the diagnosis of ID is thought to reflect a relationship between intellectual and everyday functioning, and most studies identify borderline intellectual disability solely from intellectual functioning measures, i.e., BIF (29). While the current study found disparities in the associated clinical features between the BIF and non-BIF patients with pSUD, the differences were primarily reserved to the SCL-90-R GSI score. Surprisingly, the findings thus did not support the presence of a more global impairment in BIF compared to non-BIF patients with pSUD. e.g., educational attainment is typically shown to be associated with higher intellectual functioning (81–83). However, to access specialized treatment for SUDs within the Norwegian public health service, patients must exhibit severely debilitating substance use. Furthermore, both the BIF, and non-BIF groups share approximately the same early onset of substance use (13 years). Both early onset and subsequent severe substance use likely attenuate the predictive value of IQ by exerting a major detrimental influence on scholastic performance (84), attendance (85), drop out (86–89), and overall social adjustment.

The present study used the classification of BIF rather than borderline intellectual disability, as the latter relies on additional measures of adaptive functioning and onset before 18 years of age. In addition, several studies investigated the clinical features of co-occurring BIF and SUD by combining the IQ ranges of BIF and mild ID (2, 24, 35, 90, 91). The risk factors and associations identified in these studies may result from the inclusion of a proportion of individuals with ID. Alternatively, our results

may be used to argue that intellectual functioning, as measured by WASI or otherwise, may be less useful when accounting for differences in clinical features and everyday functioning in patients with SUD.

Strengths and Limitations

The current cohort was recruited from a multitude of specialized and diversified SUD rehabilitation services including both in- and out-patient units targeting different patient groups with regard to type and severity of comorbid psychiatric disorders, the severity of substance use, and degree of social adjustment and functioning, as well as the stage of the rehabilitation process. The universal access to health care in Norway allows the collection of a more comprehensive sample relative to countries where care is privatized and costly. Thus, the findings of the current study cannot necessarily be generalized to a specific clinical population (e.g., in-patients), but do elucidate the general state of intellectual functioning and associated clinical features among patients with pSUD.

Most previous studies investigated the clinical features of individuals with substance use among patients already identified as having ID (IQ < 70) or MBID (IQ = 50–85) (2). To the authors knowledge, this study is the first to examine the prevalence rates and associated demographic and clinical factors in individuals with previous unidentified BIF (IQ = 70–85) in both in- and out-patients receiving mainstream SUD services for polysubstance abuse. The current study's main findings are consistent with the few other studies from a SUD population, who identify an over-representation of impaired intellectual function among patients with SUD (24, 29). The current study adds on to these results by controlling for the effect of age, gender, years of education, age of onset of substance use, history of injecting drugs and satisfaction with life, in the analysis of the association between BIF and psychological distress.

The main limitation of this study concerns the representativeness of the Norwegian WASI test norms. Previous studies have shown that WASI tends to overestimate the FSIQ IQ level in Norwegian samples (92, 93), which may have led to the underestimation of the prevalence rate of BIF in the current study. In addition, the clinical differences between the BIF and non-BIF groups in the sample may have been masked if a skewed cut-of value of BIF have led to inclusion of non-BIF patients within the BIF group. Furthermore, WASI has not explicitly been validated for patients with SUD with a high level of psychological distress, which may also have affected the results of the present study. Finally, the STAYER cohort was recruited using convenience sampling in a clinical setting, which is vulnerable to ascertainment biases by undersampling patients with lower intellectual functioning, low motivation for change and lower-functioning patients with BIF.

Clinical Implications

BIF among patients with SUD is common. Screening for intellectual functioning should therefore always be considered as part of the clinical practice, and treatment programs should account for a significant sub-population of patients with co-occuring SUD and intellectual impairments.

Clinicians should not only be wary of elevated levels of psychological distress in patients with SUD (54), but also that BIF may represent a potential added risk factor for detrimental treatment outcomes, drug-seeking behavior and relapse. Studies aimed at examining potential factors that mediate and moderate the relationship between psychological distress and intellectual functioning are therefore strongly warranted.

The current study could not establish a relationship between BIF status and social adjustment, which further highlights the importance of including data pertaining to everyday functioning in the assessment and diagnosis of ID, as well as the classification of borderline intellectual disability. Conjointly, measurements of general intellectual functioning may, to a lesser degree, predict social adjustment in patients with SUD. Furthermore, the associated risk factors as well as the long-term rehabilitation trajectories and prognosis of the co-occurrence of SUD and BIF are mostly unknown and warrant further investigation.

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 Regional Ethics Committee (REK 2011/1877). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH, EH, and AE: conceptualized and designed the study. JH: wrote the first draft and revised the manuscript. JH and AE: performed the analyses. AE, EH, KB, and AL: made critical revisions of the manuscript. AE and AL: supervised the study. All authors contributed to the article and approved the submitted version.

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

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A "Good" Smoke? The Off-Label Use of Cannabidiol to Reduce Cannabis Use

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Background: Although cannabis use is common in France, it is still criminalized. Cannabidiol (CBD) products, including CBD-rich cannabis, are legally available. Although previous results suggested that CBD may have benefits for people with cannabis use disorder, there is a lack of data on cannabis users who use CBD to reduce their cannabis consumption. We aimed to identify (i) correlates of this motive, and (ii) factors associated with successful attempts to reduce cannabis use.

Methods: A cross-sectional online survey among French-speaking CBD and cannabis users was conducted. Logistic regressions were performed to identify correlates of using CBD to reduce cannabis consumption and correlates of reporting a large reduction.

Results: Eleven percent ($n = 105$) of our study sample reported they primarily used CBD to reduce cannabis consumption. Associated factors included smoking tobacco cigarettes (adjusted odds ratio (aOR) [95% confidence interval (CI)] 2.17 [1.3–3.62], $p = 0.003$) and drinking alcohol (aOR [95%CI] 1.8 [1.02–3.18], $p = 0.042$). Of these 105, 83% used CBD-rich cannabis to smoke, and 58.7% reported a large reduction in cannabis consumption. This large reduction was associated with non-daily cannabis use (aOR [95%CI] 7.14 [2.4–20.0], $p < 0.001$) and daily CBD use (aOR [95%CI] 5.87 [2.09–16.47], $p = 0.001$). A reduction in cannabis withdrawal symptoms thanks to CBD use was the most-cited effect at play in self-observed cannabis reduction.

Conclusions: Cannabis use reduction is a reported motive for CBD use—especially CBD-rich cannabis to smoke—in France. More studies are needed to explore practices associated with this motive and to accurately assess CBD effectiveness.

Keywords: cannabidiol (CBD), cannabis (marijuana), cannabis use disorder (CUD), smoking, France, harm reduction

INTRODUCTION

Cannabis use is being increasingly liberalized worldwide (1), and cannabidiol (CBD) products are proliferating (2). Recent trends in Europe and the U.S. suggest an increase in the prevalence of cannabis use disorders (CUD) (3–5), for which there is still no approved pharmaceutical treatment. Preliminary data have highlighted that CBD has benefits in CUD treatment (6). Evidence is also growing that nabiximols—an oromucosal spray providing a balanced mixture of tetrahydrocannabinol (THC) and CBD—brings benefits in CUD treatment (7–11). However, little is known about cannabis users who use CBD to reduce their cannabis use (12).

Cannabis use is still criminalized in France, including for therapeutic purposes. Users may be punished by up to 1 year in prison and a fine of 3,750 € (13); since 2020, an on-the-spot fine of 150 € can replace the normal procedure at the police's discretion (14). Despite this criminalization, France has the highest prevalence of cannabis use among young people and adults in Europe (15), and indicators of cannabis use disorder and treatment for dependence are on the rise (16). The demand for herbal cannabis is also growing, as is its potency (17). A similar trend in increasing potency has been observed internationally (18, 19).

Despite strong development of the CBD market internationally—including in France—in recent years (2), the legal status of CBD products still remains unclear. Recent rulings by the Court of Justice of the European Union (20) and the French Court of Cassation (21) confirmed that CBD products legally produced in the European Union can be sold in France. The legal status of cannabis flowers with <0.2% of THC—which are widely marketed in France—is still unclear.

Given this context, we aimed to investigate whether some French CBD users consume this phytocannabinoid to reduce cannabis consumption, and to identify potential correlates for this motive. We also aimed to document the pattern of CBD use associated with this motive, and to describe the effects at play in reducing cannabis consumption, as reported by users.

MATERIALS AND METHODS

Data Collection

An online survey written in French was conducted using a Google form between April 23, 2020 and March 30, 2021. The protocol followed the guidelines of the Declaration of Helsinki, and the INSERM Ethics Committee provided ethical approval (approval #20-677 dated April 23, 2020). A link to the survey was distributed *via* media outlets specializing in cannabis-based products, CBD user groups on Facebook, and a community of people with chronic health conditions. Inclusion criteria for the present study were: previous-month CBD use and lifetime illegal cannabis use.

In the survey, the acronym "CBD" was used to include all legal products marketed as containing a significant amount of CBD, irrespective of their actual CBD content. This therefore covered legal CBD-rich THC-low (<0.2%) cannabis to smoke (called "CBD-rich cannabis" in this manuscript), as opposed to "regular" high THC cannabis (called "illegal cannabis" here). The survey collected self-reported data on the following: socio-demographic and substance use (cannabis, CBD, alcohol, tobacco) characteristics, preferred mode of CBD use, and primary reason for CBD use. The latter was collected using the question "In the past 30 days, why have you used CBD?". Only one answer was allowed from a list of options which included "to reduce the use of tobacco or other substances (illegal cannabis, alcohol, etc.)" (**Supplementary Table 1**). People who ticked this answer were then asked if they used CBD for illegal cannabis use reduction. Those who replied "yes", were then asked (i) to what extent CBD had an impact on their illegal cannabis use ("large reduction/moderate reduction/no effect/moderate increase/large increase/I do not know"; these answer options were dichotomized into "large reduction" vs. "no large reduction" (i.e., all other answers)), and (ii) which CBD-related effects were involved in reducing their illegal cannabis use ("In your opinion, what CBD-related effects were at play in reducing your illegal cannabis use?"). Participants could choose several responses from the following four pre-determined options: "using less illegal cannabis in a joint," "longer time between smoking two joints of illegal cannabis." "reduction in illegal cannabis withdrawal symptoms," and "longer time before smoking first joint of the day".

Outcomes

Two principal outcomes were built. The first was "using CBD for illegal cannabis use reduction", as regarded the whole of the study sample. The second was "reporting a large reduction in cannabis consumption thanks to CBD use", and regarded only the sub-sample of respondents who answered "yes" to the question for the first outcome.

Statistical Analyses

We characterized users using CBD as a means to reduce their illegal cannabis use by comparing their socio-demographic and socio-behavioral characteristics with the rest of the sample using a Chi-square (categorical variables) or Wilcoxon's (continuous variables) test. We then performed a logistic regression with "having used CBD to reduce illegal cannabis use" as an outcome and socio-demographic and behavioral characteristics as explanatory variables (**Figure 1**). For the sub-population who reported this reason, we performed a second logistic regression with "reporting a large reduction in illegal cannabis following CBD use" as the outcome, and variables related to CBD use as explanatory variables (**Figure 1**). For both regressions, only variables with a liberal p-value < 0.20 in the univariable analyses were considered eligible for the multivariable model. The final multivariable model was built using a backward stepwise procedure. The likelihood ratio test ($p < 0.05$) was used to define the variables to maintain in the final model.

We also provided a description of the self-reported CBD-related effects at play to reduce illegal cannabis consumption, and used Chi-square tests to compare these effects between the group of participants reporting a large reduction in illegal cannabis use and those who did not.

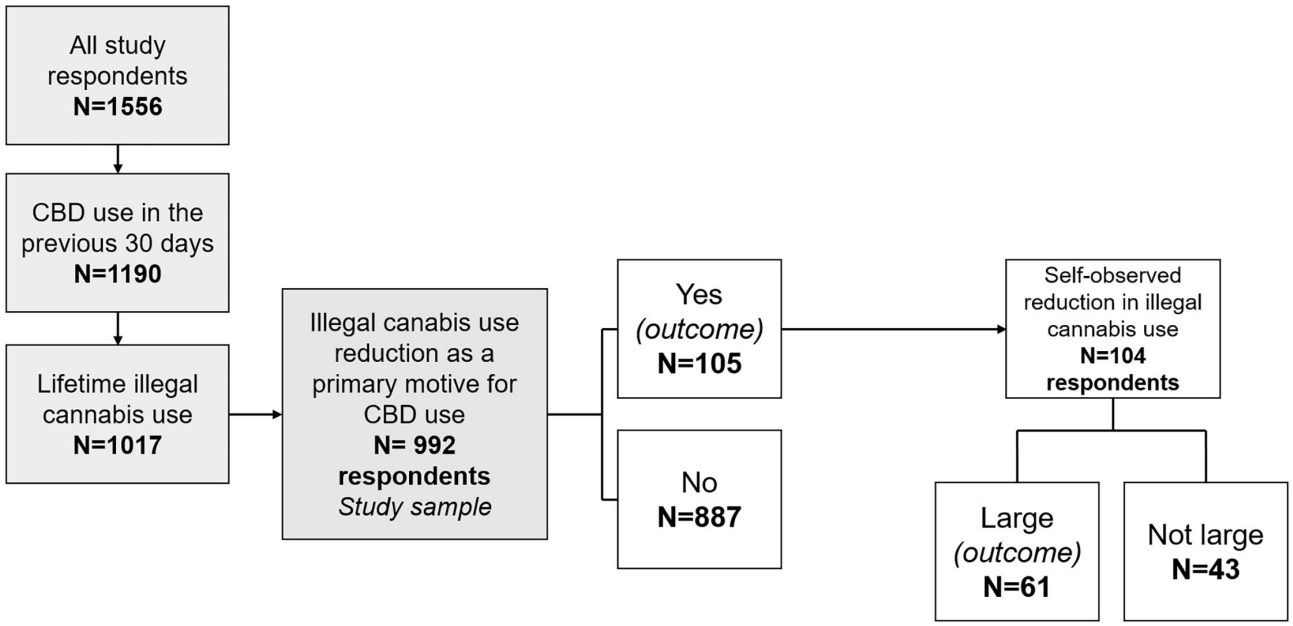

FIGURE 1 | Flow chart of the study, design of the regression outcomes, and distribution of participants according to the two study outcomes. CBD, cannabidiol.

RESULTS

Among the 1,556 respondents, 1,190 participants used CBD in the 30 days before the survey (**Figure 1**). Of the 1,017 of the latter who reported lifetime illegal cannabis use, 992 answered the question related to the primary reason why they used CBD. Study sample characteristics are provided in **Table 1**. Our study sample consisted in 992 CBD (and lifetime illegal cannabis) users. Most were men (74.5%), median age was 34 years, and most resided in France (96.5%). Over 10% (10.6% ($n = 105$)) reported having used CBD in the previous month primarily to reduce their illegal cannabis consumption. The vast majority of the study sample (99.4%) had used illegal cannabis before their first use of CBD. Among those who reported illegal cannabis reduction as their primary reason to use CBD, 66.7 and 8.8% had also used it for tobacco and alcohol use reduction, respectively.

In multivariable analysis, declaring to use CBD primarily to reduce illegal cannabis consumption was associated with younger age, tobacco cigarette smoking in the previous month, alcohol drinking in the previous month, and not having a job (**Table 1**).

Among those who declared using CBD to reduce their illegal cannabis, half (51.5%) had used CBD for less than a year, and 38.5% had used it every day in the previous month (**Table 2**). Sixty-one (58.7%) reported that their CBD use led to a large reduction in illegal cannabis consumption, 36 (34.6%) a moderate reduction, 6 (5.8%) no reduction, and 1 (1.0%) a moderate increase (1 missing value). Most (84.3%) smoked CBD-rich cannabis, while only 7.8% administered it orally (**Table 2**). A large majority (94.0%) of those who smoked CBD-rich cannabis mixed it into joints (i.e., together with tobacco or illegal cannabis).

In multivariable analysis, declaring a large reduction (vs. no large reduction) was associated with daily CBD use in the previous month, and non-daily use of illegal cannabis (**Table 2**).

The self-reported CBD-related effect involved in illegal cannabis use reduction most frequency cited was "reducing cannabis withdrawal symptoms" (44.2%), followed by "delaying first illegal cannabis joint of the day" (24.0%), "using less illegal cannabis in joints" (21.2%) and "increasing the time between smoking joints" (16.3%) (**Table 3**). Participants reporting a large reduction in illegal cannabis use were more likely to quote "reducing cannabis withdrawal symptoms" as an effect ($p < 10^{-3}$) but less likely to report "delaying first illegal cannabis joint of the day" ($p = 0.008$; **Table 3**).

DISCUSSION

In a sample of 992 CBD and lifetime illegal cannabis users mostly based in France, we found that using CBD to reduce illegal cannabis use was associated with tobacco smoking, alcohol use and not having a job. Moreover, a large self-reported reduction in illegal cannabis reduction was associated with daily CBD use and non-daily use of illegal cannabis. Finally, in users who used CBD to reduce illegal cannabis consumption, the most common route of CBD administration was smoking (84.3% of all respondents). A reduction in cannabis withdrawal symptoms was the most quoted self-reported CBD-related effect involved in cannabis use reduction (44.2%).

We found that among French CBD and illegal cannabis users, polysubstance use (tobacco and alcohol) is associated with the motivation to reduce illegal cannabis consumption. Interestingly, most of those who reported this motive also reported using CBD to try to cut down or stop tobacco use (few had done so for alcohol use). This would suggest that these CBD users commonly try to reduce their overall smoking (i.e., cannabis and tobacco) behavior. This is very interesting, given that both products are

TABLE 1 | Study sample socio-demographic and behavioral characteristics and factors associated with the use of cannabidiol to reduce cannabis consumption (logistic regression).

	CBD use to reduce or stop cannabis use			Univariable analyses		Multivariable analysis ($n = 964$)	
	No $n = 887$ **(89.4%)** ***N* (%)**	**Yes** $n = 105$ **(10.6%)** ***N* (%)**	***p*-value**[a]	**OR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Gender ($n = 984$)			0.673				
Male	653 (74.3)	80 (76.2)		1			
Female	226 (25.7)	25 (23.8)		0.9 (0.56–1.45)	0.673		
Age (years) median (IQR)	35 (28–42)	30 (25–37)	<0.001	0.95 (0.93–0.97)	<0.001	0.95 (0.93–0.97)	<0.001
Smoking tobacco cigarettes in previous 30 days ($n = 982$)			0.012				
No	306 (34.8)	21 (20.6)		1		1	
Yes	504 (57.3)	80 (78.4)		2.31 (1.4–3.82)	0.001	2.17 (1.3–3.62)	0.003
Smoking mainly e-cigarettes	70 (8.0)	1 (1.0)		0.21 (0.03–1.57)	0.128	0.23 (0.03–1.79)	0.162
Alcohol consumption in previous 30 days ($n = 973$)			0.012				
No	247 (28.4)	17 (16.7)		1		1	
Yes	624 (71.6)	85 (83.3)		1.98 (1.15–3.4)	0.013	1.8 (1.02–3.18)	0.042
Cannabis use prior to first CBD use			0.398				
No	6 (0.7)	0 (0)		-			
Yes	881 (99.3)	105 (100)		-			
High educational level[b] **($n = 954$)**			0.484				
No	281 (32.9)	36 (36.4)		1			
Yes	574 (67.1)	63 (63.6)		0.86 (0.56–1.32)	0.485		
Having a job ($n = 990$)			0.063				
No	640 (72.2)	84 (80.8)		1		1	
Yes	246 (27.8)	20 (19.2)		0.62 (0.37–1.03)	0.065	0.51 (0.29–0.89)	0.017
Housing			0.917				
Owner	301 (33.9)	33 (31.4)		1			
Tenant	433 (48.8)	55 (52.4)		1.16 (0.73–1.83)	0.527		
Living with parents or friends	111 (12.5)	12 (11.4)		0.99 (0.49–1.98)	0.968		
Prefer not to respond	42 (4.7)	5 (4.8)		1.09 (0.4–2.94)	0.871		
Self-reported income level[c]			0.394				
Below average	301 (33.9)	30 (28.6)		1			
Average	412 (46.4)	56 (53.3)		1.36 (0.85–2.18)	0.194		
Above average	174 (19.6)	19 (18.1)		1.1 (0.6–2)	0.767		

(Continued)

TABLE 1 | Continued

	CBD use to reduce or stop cannabis use			Univariable analyses		Multivariable analysis ($n = 964$)	
	No $n = 887$ **(89.4%)** ***N* (%)**	**Yes** $n = 105$ **(10.6%)** ***N* (%)**	***p*-value**[a]	**OR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Body mass index ($n = 984$)			0.022				
<25 kg/m^2	634 (72.0)	85 (82.5)		1			
≥25 kg/m^2 (overweight or obesity)	247 (28.0)	18 (17.5)		1.84 (1.08–3.12)	0.024		
Daily cannabis use in previous 30 days ($n = 978$)			0.213				
No	701 (80.2)	78 (75.0)		1			
Yes	173 (19.8)	26 (25.0)		1.36 (0.83–2.24)	0.227		
Used CBD to reduce tobacco use in previous 30 days ($n = 105$)[d]			-				
No[e]	-	35 (33.3)		-			
Yes	-	70 (66.7)		-			
Used CBD to reduce alcohol use in previous 30 days ($n = 102$)[d]			-				
No[e]	-	93 (91.2)		-			
Yes	-	9 (8.8)		-			

[a] *Chi-square (categorical variables) or Wilcoxon rank-sum test (continuous variables).*
[b] *Higher educational level was defined as attending third-level education.*
[c] *Income level was subjectively assessed using participant-perceived average income level as a reference value.*
[d] *This question was answered only by users who declared that reducing substance use was their primary reason to use CBD. This variable was not included in the regression model and is displayed for descriptive purposes only.*
[e] *Percentages are given for users who declared reducing cannabis use as the primary reason to use CBD.*
aOR, adjusted odds ratio; CBD, cannabidiol; CI, confidence interval.

commonly co-consumed (22), and that the continued use of one substance is a barrier to reducing or quitting the other (23) (something already documented for polysubstance use (24, 25)).

The positive association between not having a job and desire to cut down on/stop cannabis consumption through CBD use may seem counter-intuitive given that cannabis is frequently used to cope with stress, and that unemployment is linked with stress. Two hypotheses can be made to explain this association. The first is that the desire to reduce cannabis use may be the result of losing one's job because of cannabis use (26, 27). The second is that unemployed persons may desire to cut down on cannabis-related expenditures because of financial difficulties. Indeed, previous work highlighted that unemployed cannabis buyers were more likely to spend a larger part of their income on cannabis (28). However, as a large majority of the whole study sample was unemployed, this result we found may also be a consequence of biased participant sampling.

We found that a large reduction in illegal cannabis consumption was associated with daily CBD use, which suggests a dose-dependent effect of CBD. This relationship was not observed for high CBD doses (400 and 800 mg) in a phase 2a placebo-controlled randomized trial (6). However, it is possible that having multiple intakes per day enables users to maintain stable CBD plasma levels—and physiological effects—throughout the day. After inhalation, CBD plasma peak is attained within 10 min, with a half-life of ∼30 h (29). Moreover, the fact that non-daily illegal cannabis users were more likely to declare a large reduction in cannabis use suggests that the higher the frequency of cannabis use, the more difficult it is to change one's cannabis use pattern; this is probably related to cannabis dependence. In studies elsewhere, the frequency of cannabis flower use was associated with problematic cannabis use (30), the frequency of high-potency cannabis use predicted greater dependence (31), and greater monthly THC exposure was associated with more symptoms of dependence (32).

A few elements in our analysis suggest that CBD-rich cannabis was partially substituted for illegal cannabis in our study sample. First, in the group that used CBD to reduce illegal cannabis use, a majority smoked CBD-rich cannabis. Second, only 6% of the latter smoked "pure" (i.e., non-mixed) CBD-rich cannabis, which means that in almost all cases, it was mixed with either tobacco or illegal cannabis. Third, over 20% of the sub-sample which used

TABLE 2 | Cannabidiol products pattern of use among users who used cannabidiol to reduce illegal cannabis consumption, and factors associated with a large reduction in illegal cannabis consumption.

	Large reduction in illegal cannabis use			Univariable analyses		Multivariable analysis ($n = 103$)	
	No $n = 43$ **(41.4%)**	**Yes** $n = 61$ **(58.6%)**	***p*-value**[a]	**OR (95% CI)**	***P*-value**	**aOR (95% CI)**	***P*-value**
	***N* (col %)**	***N* (col %)**					
Time since first CBD use			0.858				
Less than a year	21 (48.8)	32 (53.3)		1			
Between 1 and 2 years	10 (23.3)	14 (23.3)		0.92 (0.34–2.45)	0.865		
More than 2 years	12 (27.9)	14 (23.3)		0.77 (0.3–1.97)	0.581		
Daily CBD use in previous 30 days			<0.001				
No	36 (83.7)	28 (45.9)		1		1	
Yes	7 (16.3)	33 (54.1)		6.06 (2.34–15.73)	<0.001	5.87 (2.09–16.47)	0.001
CBD purchase locations in previous 30 days			0.326				
On the internet	12 (27.9)	12 (19.7)		1			
Other	31 (72.1)	49 (80.3)		1.58 (0.63–3.96)	0.328		
Principal mode of CBD administration in previous 30 days			0.213				
Smoked (combustion)	37 (88.1)	49 (81.7)		1			
Inhalation	1 (2.4)	7 (11.7)		5.29 (0.62–44.85)	0.127		
Other (infusion, ingestion)	4 (9.5)	4 (6.7)		0.76 (0.18–3.22)	0.704		
CBD price per gram during most recent purchase			0.569				
<5€	10 (25.6)	12 (20.7)		1			
Between 5 and 9€	20 (51.3)	36 (62.1)		1.5 (0.55–4.08)	0.427		
10€ or more	9 (23.1)	10 (17.2)		0.93 (0.27–3.17)	0.902		
Previous month CBD budget			0.287				
<40€	9 (21.4)	14 (24.1)		1			
Between 41 and 100€	23 (54.8)	23 (39.7)		0.64 (0.23–1.78)	0.395		
More than 100€	10 (23.8)	21 (36.2)		1.35 (0.44–4.16)	0.601		
Daily cannabis use in the previous 30 days			<0.001				
No	23 (53.5)	54 (90)		1		1	
Yes	20 (46.5)	6 (10.0)		0.13 (0.05–0.36)	<0.001	0.14 (0.05–0.42)	<0.001
Smoked pure CBD[b]			0.046				
No[c]	36 (100)	43 (89.6)		-			
Yes	0 (0)	5 (10.4)		-			

[a] *Chi-square (categorical variables) or Wilcoxon rank-sum test (continuous variables).*

[b] *This question was answered only by users who declared smoking CBD. This variable was not included in the regression model and is displayed for descriptive purposes only.*

[c] *Percentage is given for users who declared smoking as their principal mode of CBD administration in previous 30 days.*

aOR, adjusted odds ratio; CBD, cannabidiol; CI, confidence interval.

CBD to reduce their illegal use declared that it helped them use less illegal cannabis in their joints.

The substitution practice mentioned above should be considered in the context of cannabis use disorder treatment and associated psychiatric outcomes. For example, replacing high-potency cannabis with CBD-rich cannabis would mean a reduction in THC exposure while preserving the gesture and the sensory dimensions of cannabis use. This reduction would likely reduce anxiety and depression in people with cannabis use disorder (33, 34), and be an acceptable and therefore achievable treatment goal for treatment-seeking users (35). Such a reduction in exposure to THC may also lead to cannabis abstinence. These various possibilities need to be clinically tested.

The dominance of smoked CBD-rich cannabis (i.e., as opposed to oral intake) in our study sample is of particular interest, as in France, CBD-rich cannabis is the only cannabis legally available. The global tendency of rising THC levels (i.e., higher potency) and decreasing CBD levels in illegal cannabis (17–19) comes fuel concerns over cannabis use-related harms, as THC is the compound responsible for cannabis use disorder (36, 37). Highly-potent cannabis consumption has been associated with higher risks of cannabis use problems and anxiety disorders (38) as well as psychosis (39, 40). Conversely, CBD seems to attenuate THC-related psychotic-like effects, memory problems (especially in light users), paranoia, anxiety and cannabis-related psychological wellbeing impairment (41–44). This could be due to functional interactions between THC and CBD (45). However, more research is needed to fully elucidate how CBD influences the effects of THC (46). Low-potency cannabis has been described as being one way to reduce cannabis-related health risks (avoiding daily use and combusted cannabis inhalation being two other ways) (47). Accordingly, for cannabis users in France—a population which must choose between illegal high-potency and legal CBD-rich cannabis—mixing both products may be a way for them to create low-risk cannabis, or to move toward creating a "smoking version" of nabiximols. Accordingly, Gibson et al., in the U.S., found that THC + CBD chemovar (9% THC, 10% CBD, from local and legal dispensary) was associated with similar levels of positive subjective effects, but significantly less paranoia and anxiety, as compared to the THC-dominant chemovar (44).

A recent U.S. study also found that CBD and cannabis co-users reported a high proportion of CBD smoking administration (48).

Given that CBD-rich cannabis is sold as the same type of product (i.e., in herbal form) as illegal cannabis, it can be incorporated into one's smoking habits. Moreover, results from previous studies on tobacco smokers suggested that the sensations which smoking creates in the airways contribute to short-term satisfaction, the rewarding effect, and reduced craving (49–51). One can therefore suppose that smoking CBD-rich cannabis may be "beneficial" as part of a strategy to lower exposure to THC: by preserving the smoking-related airway sensation as well as the terpene-related taste (52–54), a minimal reduction in the satisfaction experienced from the act of smoking may be derived from THC-low cannabis as compared to THC-high cannabis (44). In reality, smoking cannabis exposes persons to harmful substances, including carcinogens (55–57). This route of administration is therefore inadvisable, in favor of smoke-free inhalation (58) or oromucosal administration (29).

TABLE 3 | Self-reported CBD-related effects at play in cannabis use reduction.

	All	Large cannabis use reduction		
	n = 104	No *n* = 43 (41.4%)	Yes *n* = 61 (58.7%)	*p*-value[a]
Using less illegal cannabis in a joint				0.057
No	82 (78.8)	30 (69.8)	52 (85.2)	
Yes	22 (21.2)	13 (30.2)	9 (14.8)	
Longer delay between two joints of illegal cannabis				0.601
Non	87 (83.7)	35 (81.4)	52 (85.2)	
Yes	17 (16.3)	8 (18.6)	9 (14.8)	
Reduction in illegal cannabis withdrawal symptoms				<0.001
No	58 (55.8)	34 (79.1)	24 (39.3)	
Yes	46 (44.2)	9 (20.9)	37 (60.7)	
Longer time before smoking first joint of the day				0.008
No	79 (76.0)	27 (62.8)	52 (85.2)	
Yes	25 (24.0)	16 (37.2)	9 (14.8)	

[a] *Chi-square test.*

Our study has several limitations. First, the non-representativeness of our sample of cannabis users in France limits the generalizability of our results, and highlights the need for study duplication. For instance, participants with no job appeared over-represented. Second, we had no data to enable us to detect cannabis use disorder in our sample. However, we did have frequency of use data, which is a good proxy for problematic and low-risk cannabis use (47, 59, 60). Third, we used self-assessed changes (reduction/no change/increase) in cannabis use and had no data on the contextual elements of these changes. Accordingly, we were not able to deduce to what extent CBD was clinically useful in attempts to cut down on cannabis use. Finally, data on the levels of CBD in products consumed by the participants were not available, which limits the solidity of our conclusions. CBD content is highly variable among different products, including cannabis flowers (61–63). For instance, in a large Italian study on THC-low cannabis products, authors found a mean CBD concentration of 4% in the sub-sample ($n = 185$) of flowers with a THC level under 0.2% (i.e., which would be legal in France), with a strong linear correlation between CBD and THC concentrations (personal communication from (64)). As in the survey "CBD" refers to all CBD-based products irrespective of their actual CBD content, answers given by participants may refer to the use of CBD-low products (e.g., THC-low CBD-low legal cannabis flowers or oil

with low CBD concentration). Therefore, the effects we reported should be cautiously attributed to CBD-rich cannabis/products.

The main strength of our study is the explorative and original nature of the data; while the use of CBD and CBD-rich cannabis has previously been reported for opioid and pain medication substitution in people with fibromyalgia (65), and the use of nabiximols clinically investigated elsewhere (7), to the best of our knowledge, the substitution of illegal cannabis with CBD has not been previously investigated.

Our findings have many implications. First, we found that some CBD users in France are using the phytocannabinoid in an "off-label" fashion to reduce their illegal cannabis consumption. Further studies should be implemented to confirm and quantify to what extent CBD or nabiximols can in fact accomplish this task. Second, in countries where cannabis use is criminalized but not CBD-rich cannabis, the latter may represent an acceptable tool for THC-related harm reduction. With this in mind, any ban on smokable CBD products could reduce the number of consumers able to reduce their illegal cannabis consumption through CBD use. Bans could also prevent people who smoke cannabis for therapeutic purposes from adjusting their THC/CBD ratio to optimize benefits (62). Finally, non-smoking (e.g., oromucosal) routes of CBD administration to users who wish to reduce their cannabis consumption should be promoted to reduce health-related risks.

To conclude, CBD is used by some illegal cannabis users in France—especially alcohol and tobacco co-users—who wish to reduce their cannabis consumption. In our study, CBD was mainly smoked (i.e., CBD-rich cannabis), and seemed to contribute to cannabis use reduction by lowering cannabis withdrawal symptoms. More studies are needed to explore practices associated with CBD use to reduce cannabis consumption, and to accurately assess its effectiveness.

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 study was reviewed and approved by INSERM Ethics Committee provided ethical approval (approval #20-677 dated April 23, 2020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DF designed the study, interpreted the data, and reviewed the manuscript. VD performed the statistical analyses. SM, YB, and PC designed the study and reviewed the manuscript. TB interpreted the data and wrote the manuscript draft and reviewed it. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.829944/full#supplementary-material

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A History of Childhood Maltreatment Has Substance- and Sex-Specific Effects on Craving During Treatment for Substance Use Disorders

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Rationale: Childhood maltreatment (CM) leads to detrimental mental health outcomes, such as substance use disorders (SUD). This study examined prevalence and severity of all five types of CM with respect to specific substances and sex in treatment-seeking individuals with SUD. The influences of type of CM and symptoms of depressiveness, anxiety, and perceived stress on substance craving at admission as well as craving reduction during SUD treatment were examined.

Methods: *N* = 546 patients in treatment for SUD and *N* = 109 individuals in opioid maintenance treatment filled out questionnaires regarding CM (Childhood Trauma Questionnaire) and psychopathologies. Substance craving was assessed throughout treatment using the Mannheim Craving Scale. Group differences in CM, type of substance and sex were examined. General linear models were applied to examine influences on substance craving.

Results: Higher prevalence and severity of all five subtypes of CM were observed in individuals with SUD compared to the general population. Women were more severely affected by emotional and sexual abuse than men. Patients with cannabis use disorder reported more severe experiences of emotional abuse compared to all other substances. Craving at admission to treatment was influenced by emotional abuse, however, symptoms of depressiveness, anxiety, and perceived stress contributed to craving at admission or craving reduction during treatment.

Conclusion: CM relates to SUD and should be incorporated in prevention and treatment of SUD. Underlying mechanisms of the association might relate to impairments in processing and regulation of stress, emotions, and interpersonal relations following a history of CM.

Keywords: childhood trauma, addiction, sex differences, substance craving, substance use disorder, perceived stress, addiction treatment

INTRODUCTION

A variety of studies examined the consequences of adverse childhood experiences (ACE) that are related to the development of somatic and mental disorders (1). ACE are defined as household dysfunction but also childhood maltreatment (CM) (2, 3). Specifically, CM is operationalized as emotional, physical, and sexual abuse as well as emotional and physical neglect (4). A history of CM is related to the age of onset and severity of subsequent mental disorders, and reduces treatment response (4–9).

In Europe, high prevalence rates of CM have been reported for the general population: 29.1% for emotional abuse, 22.9% for physical abuse, 13.4% (female) and 5.7% (male) for sexual abuse, 16.3% for physical neglect and 18.4% for emotional neglect (10). Figures for Germany are comparable, between 6.5% for at least moderate emotional abuse and 22.4% for at least moderate physical neglect (11).

A history of CM is frequently observed in individuals with substance use disorders (SUD) (12–16). It increases the risk of developing a SUD (13, 17–19), and this extends also to non-substance use disorders such as problematic and pathological gambling (20, 21). Compared to the general population in Germany (22), individuals with SUD have experienced more severe forms of CM (23). For example, the prevalence in individuals with opioid use disorder (OUD) ranges between 16% for sexual abuse in men and 43% for emotional abuse (15).

Since prevalence number of SUD and relapse rates after SUD treatment are high [e.g., (24–26)], examining factors contributing to the development and maintenance of SUD are still of importance. A stable, mostly correlational, relation has been observed between CM and different kinds of SUD even after correction for comorbid psychiatric disorders and sociodemographic variables (27). The age of drinking onset was 1 year earlier in individuals with CM (28). Furthermore, exposure to several CM predicted SUD in young adults, irrespectively of sociodemographic variables (e.g., sex or ethnicity) and after controlling for prior mental disorders (29). Similarly, a cumulative effect of the number of types of CM events was observed regarding the severity of alcohol use disorder (AUD) (30). Regarding all five sub-types of CM, emotional abuse is the strongest predictor for the severity of AUD, followed by physical abuse (31). Further, women with CM, compared to women without CM or men, were observed to have a shorter timespan between onset of drinking and AUD and lower rates of abstinence after AUD treatment were associated with CM (28, 32). Contributing to this relation, it has been observed, that the association between cumulative CM and SUD was partly mediated by mood- and anxiety disorders that preceded SUD (33).

Besides CM being associated with SUD, substance craving contributes to relapse (34–37) and, thus, maintenance of the disorder. Further, an effect of stress on substance craving was observed for methadone (38), cocaine (39), or alcohol (40), possibly linking CM, if seen as early life stress, to craving and relapse (41).

Despite the above-mentioned impact of CM on characteristics of SUD, to our knowledge no study examined CM in individuals seeking treatment for SUD while directly comparing different SUDs, investigating sex effects, or addressing the influence of the type of CM on substance craving.

Within the current project we hypothesized that (1) in individuals with SUD, prevalence of all forms of CM is higher in individuals with OUD compared to all other substances; that (2) the severity of CM is strongest in individuals with OUD compared to all other substances. For both (1, 2) women are more severely affected than men. We further hypothesize that (3) in SUD, the severity of CM is positively associated to the severity of depressive and anxious symptoms, and perceived stress; that (4) emotional abuse followed by physical abuse are predictors for the severity of craving at admission to SUD treatment; and that (5) experiences of emotional abuse and physical abuse hamper the decrease of substance craving during SUD treatment while sex and type of SUD but not age exert an effect on the latter two relationships (hypotheses 4 and 5).

MATERIALS AND METHODS

Procedure and Participants

The aggregated dataset (N = 655 individuals) derives from two sources. Firstly, between 2016 and 2020, individuals with different kinds of SUD (N = 546, sample 1) participated in a questionnaire-based examination during their treatment in the Clinic of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Mannheim, Germany. In either an inpatient or a day care setting they received a detoxification and a psychological SUD-related treatment including motivational and cognitive behavioral elements with the goal of continuous abstinence (42). SUD patients filled out several questionnaires at admission and once weekly during the treatment period of 24 $\pm$ 9.7 days. In case of repeated admissions during the data collection period of 2016 and 2020, the most recent admission time point was chosen. Diagnoses of substance addiction and additional comorbid mental disorders were made by trained medical staff following the International Classification of Diseases (ICD-10). Regarding SUD as described in the Diagnostic and statistical manual of mental disorders, 5th version (DSM-5) (43), substance addiction corresponds to moderate to severe SUD (44).

Secondly, data (N = 109, sample 2) from a research project including outpatients of the opioid maintenance treatment (OMT) of the Central Institute of Mental Health, Mannheim, were included to enrich the first dataset with individuals suffering from OUD. Data collection and diagnostic procedures also were performed by trained medical staff and a senior psychiatrist. A study description of sample 2 has previously been published (45).

For all individuals (samples 1 and 2), general inclusion criteria were: age over 18 years, sufficient knowledge of the German language (oral and in writing), main diagnosis of SUD and availability of data regarding the CM. Please see **Supplementary Figure 1** for details of the data collection, preparation and allocation process.

The local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany, approved the here presented study procedures (approval number 2018-531N-MA and 2018-807R-MA). Information for the first dataset (sample 1) was collected during the patients' inpatient treatment for clinical purpose and later used for retrospective analyses. Following the recommendation of the ethics committee to protect data privacy the data set was anonymized. Regarding the second dataset (sample 2), in accordance with the Declaration of Helsinki, all participants provided written informed consent prior to study participation.

Measures

As the focus of this study, all five sub-types of CM, namely emotional, physical, and sexual abuse as well as emotional and physical neglect, were assessed retrospectively using the reliable ($0.87 < \text{alpha} < 0.95$) childhood trauma questionnaire (CTQ), a previously validated self-report questionnaire that addresses the childhood up to the age of 18 years (46). All items of the German version were answered on a 5-point Likert scale ("not at all" to "very often") leading to sum scores between 5 (no CM) and 25 (severe form of CM) for each subscale, respectively (23). As reported by others (11, 47, 48), the severity of each subscale of CM was additionally described by aggregating the CTQ score for each subscale separately into none-minimal, minimal-moderate, moderate-severe and severe-extreme. Further, prevalence was calculated following Witt et al. (11). To do so, all subscales of the CTQ were dichotomized into "having experienced this form of CM" including moderate to extreme CM and "not having experienced this form of CM" including none to moderate CM. The number of overall CM was calculated by summing up affirmed, dichotomized CTQ subscales.

To characterize sample 1 (N = 546), besides assessing the main diagnosis of SUD and sociodemographic variables (e.g., age, gender, employment, marital status, and education), additional questionnaires were administered. The CTQ, Perceived Stress Scale (PSS) (49), and Fagerstrom Test for Nicotine Dependence (FTND) (50) were administered only once, at least 1 week after admission. The Beck Depression Inventory (BDI) (51, 52), Beck Anxiety Inventory (BAI) (53), and Mannheimer Craving Scale (MACS) (54) were administered at admission and every 7 days during treatment. The MACS retrospectively measures overall craving during the last 7 days independent of the substance and has shown to be highly reliable ($0.87 < \text{alpha} < 0.93$). MACS was applied at admission, after 1 and 2 weeks (at T01, T07, and T14), respectively. The reduction of craving after 2 weeks as the difference T01 minus T14 was used to address the course of the treatment. Regarding sample 2 of N = 109 OMT individuals, the same sociodemographic variables were assessed and the CTQ was administered.

Analyses and Statistics

The main SUD diagnosis was grouped into six categories: alcohol use disorder (AUD), cannabis use disorder (CUD), cocaine and stimulant use disorder (CSUD), sedative, hypnotics, or anxiolytic use disorders (SHA), opioid use disorder (OUD, sample 1 only), and opioid use disorder during opioid maintenance (OMT; sample 2 only). OMT and OUD samples were compared using independent samples t-tests and chi-square tests including available data for both samples to justify merging both data sets (samples 1 and 2, OUD + OMT) analyses including the CTQ (see **Supplementary Material**).

A sample description was created, and group differences were examined using analyses of variance (ANOVA) or Welch-Test for continuous data, and chi-square tests for dichotomous data. *Post hoc* tests included Tukey's or Games–Howell tests for ANOVAs and Welch-Tests. Adjusted z-scores and a transformation into p-values were performed using chi-square tests according to García-pérez and Núñez-antón (55). Further, the total number of additional SUD diagnoses and a dichotomous item on comorbid mental disorders (yes/no) were calculated. Relevant clinical variables (i.e., CM, substance craving, and symptoms of depressiveness or anxiety, perceived stress) were correlated pairwise (Pearson correlation) to assess bi-directional relations within the overall sample and separated by sex. General linear models (GLM, univariate) were used to assess the influences of CM and clinical variables (i.e., symptoms of depressiveness or anxiety, perceived stress) as well as sociodemographic variables (i.e., age and sex) on the SUD outcome (i.e., substance craving at admission, reduction of craving over the first 2 weeks of treatment). Descriptive and statistical analyses were performed in SPSS (Statistics for Windows, Version 27.0, IBM Corp., Armonk, NY, United States). To counteract multiple testing problems and following Storey (56) false discovery rate (FDR) using the Benjamini and Hochberg method was applied when adequate and results were reported when surviving the correction ($p < 0.05$).

RESULTS

Sample Composition

Out of N = 1,599 data sets, N = 804 data sets with information regarding the CTQ questionnaire (50%) were available. After excluding duplicate data sets due to readmission (N = 78) and individuals without a main diagnosis of SUD (N = 72), N = 655 data sets were available for subsequent analyses (41%), see flowchart in the **Supplementary Material**. Between January 2016 and December 2020, N = 655 individuals provided information regarding the CTQ and additional questionnaires. Data were collected from the day care clinic (N = 391), the inpatient treatment (N = 136) and the outpatient opioid maintenance program (N = 109).

Participants were between 18 and 86 years of age (mean = 42.0 $\pm$ 13.0). They were mostly male (73.3%), single (51.0%) and had no children (40.9%). They received primary and secondary education of 12.8 years, but more than half were currently not steadily employed (57.4%). The majority of participants were tobacco smokers (74.8%). In sample 1, 66.7% (N = 364) were diagnosed with AUD as the main diagnosis, 21.6% (N = 118) with CUD, 7.8% (N = 43) with CSUD, 2.2% (N = 12) with SHA, and 1.6% (N = 9) with OUD, respectively. Sociodemographic and clinical variables differed between substance groups. See **Tables 1**, **2** for more details regarding sociodemographic and clinical information.

TABLE 1 | Sociodemographic data of the overall sample.

	AUD	CUD	CSUD	SHA	OUD + OMT	Descriptive statistics
N	364 (55.6%)	118 (18.0%)	43 (6.6%)	12 (1.8%)	118 (18.0%)	655
Age	**47.23 (12.66)^{1,2,3}**	**28.6 (7.5)^{1,4,5,6}**	**33.3 (7.2)^{2,4,7,8}**	**42.9 (9.7)^{5,7}**	**42.1 (8.1)^{3,6,8}**	***F*(4,68.6) = 103.59, *P* < 0.00**
Gender (male, %)	74.2	73.7	74.4	58.3	71.2	$\chi^2(4) = 0.90$, $p = 0.824$
Family status (single yes, %)	37.6	78.0	69.8	50.0	65.7	**$\chi^2(4) = 69.30$, $p < 0.001$[a]**
Children (yes, %)	42.0	22.9	32.6	28.6	46.5	$\chi^2(4) = 16.38$, $p < 0.001$[a]
Years of education	**13.5 (2.7)^{1,2,3}**	**12.4 (2.6)^{1,4}**	**12.2 (2.6)^{2}**	13.8 (2.9)	**11.3 (2.4)^{3,4}**	***F*(4,561) = 14.90, *p* < 0.001**
Employed (yes, %)	36.8	31.4	23.3	22.2	19.7	**$\chi^2(4) = 22.60$, $p < 0.001$[a]**

Mean values (standard deviation) or percentage values are displayed. Group differences are highlighted. N, total sample size; AUD, alcohol use disorder; CSUD, cocaine and stimulant use disorders; CUD, cannabis use disorder; SHA, sedative, hypnotics, or anxiolytic use disorders; OUD + OMT, opioid use disorders + opioid maintenance treatment. [1,2,3,4,5,6,7,8]Superscripted numbers describe significant group differences following post hoc tests. [a]Following post hoc testing including correction for multiple comparison, no statistically significant group-differences emerged. Significant results are highlighted in bold.

TABLE 2 | Clinical data of sample 1.

Sample 1	AUD	CUD	CSUD	SHA	OUD	Descriptive statistics
N	364	118	43	12	9	546
Type of stay (inpatient:day care-clinic, %)	26.9:73.1	21.2:78.8	20.9:79.1	58.3:41.7	44.4:55.6	**$\chi^2(4) = 9.70$, $p = 0.021$[a]**
Mental comorbidities, current (yes, %)	47.5	51.7	48.8	66.7	88.9	$\chi^2(4) = 7.72$, $p = 0.103$
Mental comorbidities, lifetime (yes, %)	56.6	56.8	55.8	75.0	88.9	$\chi^2(4) = 5.33$, $p = 0.255$
Total number of SUD, current	**1.8 (0.9)^{1,2}**	**2.5 (1.0)^{1}**	**2.7 (1.2)^{2}**	2.8 (1.3)	3.1 (1.4)	***F*(4,33.4) = 14.94, *p* < 0.000**
Total number of SUD, lifetime	**2.0 (1.0)^{1,2}**	**2.7 (1.1)^{1}**	**3.2 (1.4)^{2}**	2.8 (1.5)	3.1 (1.4)	***F*(4,33.5) = 14.87, *p* < 0.001**
Smokers (yes, %)	59.6	79.7	65.1	75.0	93.2	**$\chi^2(4) = 54.62$, $p < 0.001$[a]**
FTND of smokers[b]	5.3 (2.4)	4.9 (2.2)	5.3 (2.0)	5.0 (1.8)	5.6 (1.4)	$F(4,359) = 0.494$, $p = 0.740$
BDI at admission	**18.9 (11.8)^{1}**	**25.2 (12.0)^{1}**	21.1 (11.5)	29.2 (10.2)	25.2 (12.0)	***F*(4,466) = 6.94, *p* < 0.001**
BAI at admission	**16.9 (13.0)^{1}**	19.4 (13.0)	**15.9 (10.2)^{2}**	**31.5 (11.0)^{1,2}**	19.4 (13.0)	***F*(4,459) = 3.49, *p* = 0.008**
PSS[b]	**20.8 (6.3)^{1}**	**23.5 (5.4)^{1}**	22.5 (5.8)	24.4 (5.4)	23.5 (5.4)	***F*(4,406) = 4.08, *p* = 0.003**
MACS at admission	**16.6 (9.8)^{1,2}**	**20.4 (10.2)^{1}**	**21.0 (9.4)^{2}**	25.0 (8.9)	19.8 (7.7)	***F*(4,467) = 5.27, *p* < 0.001**

Mean values (standard deviation) or percentage values are displayed for the clinical sample only. Group differences are highlighted. n, sample size; AUD, alcohol use disorder; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CSUD, cocaine and stimulant use disorders; CUD, cannabis use disorder; FTND, Fagerstrom Test for Nicotine Dependence; MACS, Mannheimer Craving Scale; SHA, sedative, hypnotics, or anxiolytic use disorders; SUD, substance use disorder; OUD, opioid use disorders; PSS, perceived stress scale. [1,2]Superscripted numbers describe significant group differences following post hoc tests. [a]Following post hoc testing including correction for multiple comparison, no statistically significant group-differences emerged. [b]Only administered once. Significant results are highlighted in bold.

Prevalence and Severity for All Sub-Types of Childhood Maltreatment With Respect to Different Kinds of Substance Use Disorders

Over all substances, prevalence rates of CM were 19.1% for sexual abuse, 19.8% for physical abuse, 24.7% for emotional abuse, 54.7% for physical neglect, and 67.9% for emotional neglect. Individuals with SUD experienced on average 1.90 (1.46) of five types CM, and significant group differences between substances emerged [$F(4,540) = 4.48$, $p = 0.001$]. *Post hoc* tests indicated a significant difference in the number of CM between AUD [on average 1.71 (1.42) CM] and CUD [on average 2.38 (1.44) CM].

Within the overall sample, severity of CM [mean of sum scores (standard deviation)] resulted in 6.2 (3.5) for sexual abuse, 7.7 (4.4) for physical abuse, 8.8 (3.6) for physical neglect, 10.0 (5.4) for emotional abuse, and 13.2 (5.7) for emotional neglect. Significant group differences with respect to the main diagnosis were observed for emotional abuse [$F(4,622) = 14.29$, $p < 0.001$] and physical abuse [$F(4,52.5) = 5.09$, $p = 0.001$]. *Post hoc* tests indicated significantly more severe experience of emotional abuse for CUD compared to AUD and OUD, and, additionally, of emotional neglect for CUD compared to AUD. See **Table 3** for details regarding prevalence for and severity of specific subtypes of CM in different substances.

Sex Differences in Prevalence and Severity of Childhood Maltreatment

Over all substances, females in comparison to males reported significantly more often having experienced emotional abuse [$\chi^2(1) = 26.31$, $p < 0.001$], physical abuse [$\chi^2(1) = 9.19$, $p = 0.002$] and sexual abuse [$\chi^2(1) = 37.71$, $p < 0.001$], but not emotional neglect [$\chi^2(1) = 0.46$, $p = 0.423$] or physical neglect [$\chi^2(1) = 1.66$, $p = 0.197$]. Depending on the main diagnosis, significant sex differences to the detriment of women became apparent for alcohol and emotional abuse [$\chi^2(1) = 14.45$, $p < 0.001$], alcohol and physical abuse [$\chi^2(1) = 7.09$, $p = 0.008$], alcohol and sexual abuse [$\chi^2(1) = 12.38$, $p < 0.001$], cannabis and emotional abuse [$\chi^2(1) = 7.28$, $p = 0.007$], cannabis and physical abuse [$\chi^2(1) = 5.94$, $p = 0.015$], cannabis and sexual

TABLE 3 | Severity of childhood maltreatment.

	AUD	CUD	CSUD	SHA	OUD + OMT	Statistics
N	364	118	43	12	118	655
CTQ sum score	**43.2 (16.6)[1]**	**51.4 (17.5)[1]**	43.7 (15.2)	42.6 (13.7)	46.9 (17.7)	***F*(4,539) = 4.96, *p* = 0.001**
Number of types of CM	**1.71 (1.42)[1]**	**2.38 (1.44)[1]**	1.70 (1.41)	1.71 (1.98)	1.99 (1.48)	***F*(4,540) = 4.48, *p* = 0.001**
CTQ emotional abuse	**9.2 (5.2)[1]**	**12.8 (6.0)[1,2]**	10.4 (5.2)	9.4 (3.9)	**9.5 (4.7)[2]**	***F*(4,622) = 14.29, *p* < 0.001**
Prevalence (yes, %)	19%	47%	28%	25%	19%	**$\chi^2(4) = 35.18$, *p* < 0.001[a]**
CTQ emotional neglect	12.7 (5.6)[1]	14.5 (5.6)[1]	13.0 (6.1)	12.7 (5.7)	13.5 (5.9)	*F*(4,625) = 2.16, *p* = 0.072
Prevalence (yes, %)	65%	78%	62%	50%	70%	$\chi^2(4) = 6.48$, *p* = 0.166
CTQ physical abuse	7.3 (4.0)	**8.2 (5.6)[1]**	7.9 (4.3)	**6.0 (1.5)[1,2]**	**8.7 (5.2)[2]**	***F*(4,52.5) = 5.09, *p* = 0.001**
Prevalence (yes, %)	16%	24%	26%	8%	27%	**$\chi^2(4) = 10.58$, *p* = 0.032[a]**
CTQ physical neglect	8.7 (3.4)	9.2 (4.0)	8.0 (3.1)	8.6 (2.8)	9.1 (3.8)	*F*(3,627) = 1.37, *p* = 0.241
Prevalence (yes, %)	54%	58%	47%	50%	56%	$\chi^2(4) = 2.413$, *p* = 0.660
CTQ sexual abuse	6.0 (3.3)	6.6 (4.0)	5.5 (1.5)	6.5 (3.7)	6.7 (4.0)	*F*(4,617) = 1.72, *p* = 0.144
Prevalence (yes, %)	15%	28%	12%	25%	25%	**$\chi^2(4) = 13.093$, *p* = 0.011[a]**

Mean values (standard deviation) or percentage values are displayed. Group differences are highlighted in bold. n, sample size; AUD, alcohol use disorder; CSUD, cocaine and stimulant use disorders; CTQ, Childhood Trauma Questionnaire; CUD, cannabis use disorder; SHA, sedative, hypnotics, or anxiolytic use disorders; OUD, opioids use disorders + opioid maintenance treatment. Prevalence numbers and the number of types of CM are reported for the dichotomized item "having experiences CM" coding "yes" for at least moderate experience of the respective subscale of CM. [1,2]Superscripted numbers describe significant group differences following post hoc tests. [a]Following post hoc testing including correction for multiple comparison, no statistically significant group-differences emerged.

abuse [$\chi^2(1) = 11.15$, $p = 0.001$] and opioids and sexual abuse [$\chi^2(1) = 9.09$, $p = 0.003$].

Over all substances, females reported more severe experiences of CM compared to men, resulting in significant sex differences for emotional abuse [$t(242.3) = -4.14$, $p < 0.001$] and sexual abuse [$t(196.3) = -4.46$, $p < 0.001$] (**Figure 1**). Sex differences regarding emotional neglect [$t(628) = -2.16$, $p = 0.034$] did not survive correction for multiple testing. Within each main diagnosis, significant sex differences to the detriment of women became apparent following two-sided *t*-tests for alcohol and emotional abuse [$t(123.0) = -3.05$, $p = 0.003$], alcohol and sexual abuse [$t(100.75) = -2.77$, $p = 0.007$], alcohol and emotional neglect [$t(155.49) = -2.24$, $p = 0.026$], cannabis and emotional abuse [$t(46.50) = -3.31$, $p = 0.002$] and cannabis and sexual abuse [$t(33.40) = 2.54$, $p < 0.001$]. Sex differences for physical neglect in individuals with CUD [$t(38.22) = -2.24$, $p = 0.031$] did not survive correction for multiple testing. See **Figure 2** for more details.

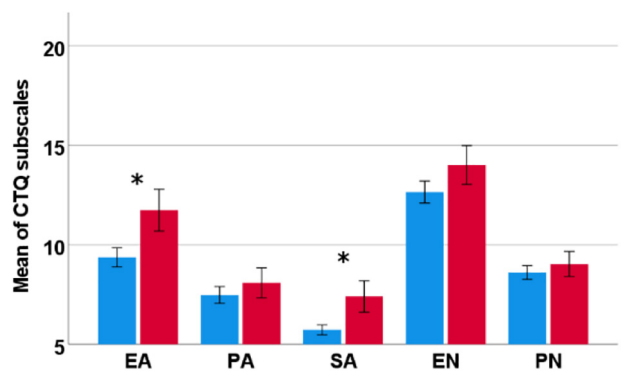

FIGURE 1 | Significant sex differences for the overall sample regarding mean values of the sum scores per subscale of the CTQ. Females (red) reported significantly more severe CM for emotional and sexual abuse than males (blue). CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse, SA, sexual abuse, EN, emotional neglect; PN, physical neglect. Error bars are displayed at a 95% confidence interval. *Significant sex difference.

Severity of Childhood Maltreatment in Relation to Symptoms of Anxiety, Depressiveness, and Perceived Stress in the Overall Patient Sample

Statistically significant positive correlations between the severity of CM (CTQ sum score) and affective symptoms were observed in the overall sample. See **Figure 3** for more details. A positive correlation between the severity of CM and BDI sum score at admission was observed for males and females (males r = 0.241, $p < 0.001$; females r = 0.251, $p = 0.012$). The correlation between severity of CM and BAI sum score at admission and PSS sum score were significant for males (BAI r = 0.248, $p < 0.001$; PSS r = 0.207, $p = 0.012$), but not females (BAI r = 0.188, $p = 0.062$; PSS r = 0.044, $p = 0.679$). See **Table 4** for more details.

The Influences of Different Types of Childhood Maltreatment on Substance Craving at Admission With Respect to Main Diagnosis and Sex

Craving at T01 (MACS T01) differed statistically significant for the different substance groups [$F(4,381) = 2.622$, $p = 0.035$, $\eta^2 = 0.027$], and sex [$F(1,381) = 6.771$, $p = 0.010$, $\eta^2 = 0.017$] after adjusting for all five subscores of the CTQ and age. Severity of emotional abuse [$F(1,381) = 17.353$, $p < 0.001$, $\eta^2 = 0.044$] but none of the other subscales of CM or age did show a significant influence. After adjusting for before-mentioned covariates, Bonferroni-corrected *post hoc* tests revealed significantly more severe craving for women ($p = 0.010$, $M_{Diff} = 2.92$, 95% CI [0.71,

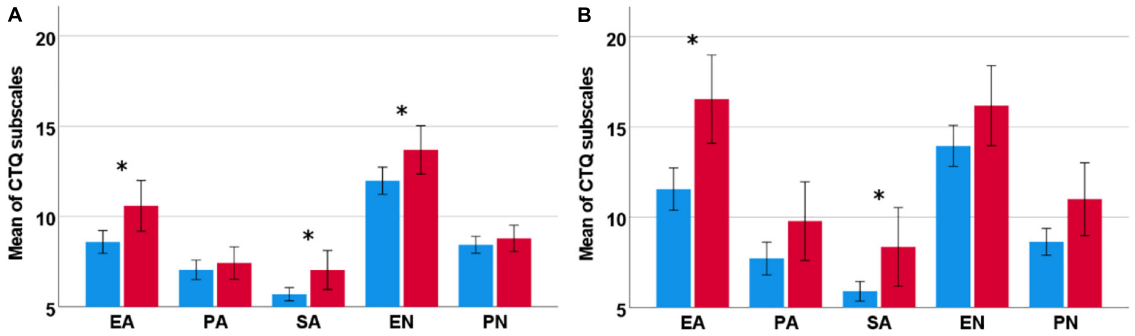

FIGURE 2 | Significant sex differences for the main diagnoses AUD (left) and CUD (right) regarding mean values of the sum scores per subscale of the CTQ. **(A)** In AUD (left), females (red) reported significantly more severe CM for emotional and sexual abuse, and emotional neglect. **(B)** In CUD (right), females (red) reported significantly more severe CM for emotional and sexual abuse. CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse, SA, sexual abuse, EN, emotional neglect; PN, physical neglect. Error bars are displayed at a 95% confidence interval. *Significant sex difference.

TABLE 4 | Severity of childhood maltreatment in relation to symptoms of anxiety, depressiveness, and perceived stress for the overall patient group, and separately by sex.

	BDI T01	**BAI T01**	**PSS**
	Corr. Coeff. | *p*-value | 1–β | *N*	Corr. Coeff. | *p*-value | 1–β | *N*	Corr. Coeff. | *p*-value | 1–β | *N*
CTQ			
All	**0.277 | <0.001 | >0.9999 | 391**	**0.259 | <0.001 | >0.9961 | 388**	**0.191 | <0.001 | >0.8393 | 351**
Males	**0.241 | <0.001 | >0.9023 | 291**	**0.248 | <0.001 | >0.8981 | 288**	**0.207 | <0.001 | >0.8641 | 261**
Females	**0.251 | <0.012 | >0.3254 | 100**	0.188 | >0.062 | – | 100	0.044 | <0.679 | – | 90

*Pearson correlation coefficients, p-values (two-sided), and power estimates are displayed. Significant correlations are highlighted in bold. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire, sum score; PSS, Perceived Stress Scale. All significant results survived correction for multiple testing (p > 0.05). Post hoc power calculations were performed in G*Power (57).*

5.12]). *Post hoc* tests regarding substance group did not yield significant results following Bonferroni correction.

After adjusting for all five subscores of the CTQ and age but also PSS, BDI (T01) and BAI (T01) sum scores, craving at T01 (MACS T01) did no longer differ statistically significant between the different substance groups [$F(4,282) = 2.516$, $p = 0.107$, $\eta^2 = 0.027$] or sex [$F(1,282) = 2.516$, $p = 0.114$, $\eta^2 = 0.009$]. Severity of emotional abuse [$F(1,282) = 1.282$, $p = 0.258$, $\eta^2 = 0.005$] did no longer show a significant influence, neither did the PSS sum score [$F(1,282) = 0.735$, $p = 0.392$, $\eta^2 = 0.003$]. BDI and BAI sum scores at admission, however, did show a significant influence [$F(1,282) = 43.637$, $p < 0.001$, $\eta^2 = 0.134$; $F(1,282) = 15.360$, $p < 0.001$, $\eta^2 = 0.052$].

The Influences of Different Types of Childhood Maltreatment on the Reduction of Substance Craving During the First 2 Weeks of Treatment With Respect to Main Diagnosis and Sex

Over all substances, craving diminished from 18.0 (10.0) at T01 to 11.0 (8.3) at T14 in the MACS questionnaire. However, no significant effect of substance group [$F(4,306) = 0.836$, $p = 0.503$, $\eta^2 = 0.011$] or sex [$F(1,306) = 3.516$, $p = 0.062$, $\eta^2 = 0.011$] was observed after adjusting for age and all five subscores of CM. There was no significant influence regarding all subscores of CM. Including PSS, BDI (T01) and BAI (T01), no significant effect of substance group [$F(4,282) = 0.341$, $p = 0.850$, $\eta^2 = 0.005$] or sex [$F(1,282) = 0.513$, $p = 0.475$, $\eta^2 = 0.002$] did emerge either. However, PSS and BDI (T01) sum scores excerpted a significant influence [$F(1,282) = 14.433$, $p < 0.001$, $\eta^2 = 0.049$; $F(1,282) = 21.050$, $p < 0.001$, $\eta^2 = 0.069$], so did age [$F(1,282) = 5.095$, $p = 0.025$, $\eta^2 = 0.018$], but not the BAI (T01) sum score [$F(1,282) = 2.807$, $p = 0.095$, $\eta^2 = 0.010$].

DISCUSSION

To our knowledge, this study is the first to examine a broad range of CM, namely emotional and physical abuse, emotional and physical neglect as well as sexual abuse in patients undergoing treatment for SUD while including several substances, such as alcohol, cannabis, cocaine and stimulant, opioid and sedative use disorders. The most salient finding of the present study was the high prevalence and severity of experienced CM in patients with CUD compared to other SUDs and especially compared to AUD. This study expands previous work on the relevance of psychosocial and biographical aspects regarding SUD.

The association between CM and SUD is well known in literature (12–21). The prevalence of moderate to extreme CM in our sample exceeded a previous estimation for the general German population ranging between 6.5% for emotional abuse and 22.4% for physical neglect (11). Similarly to the general population (11), women with SUD also reported higher

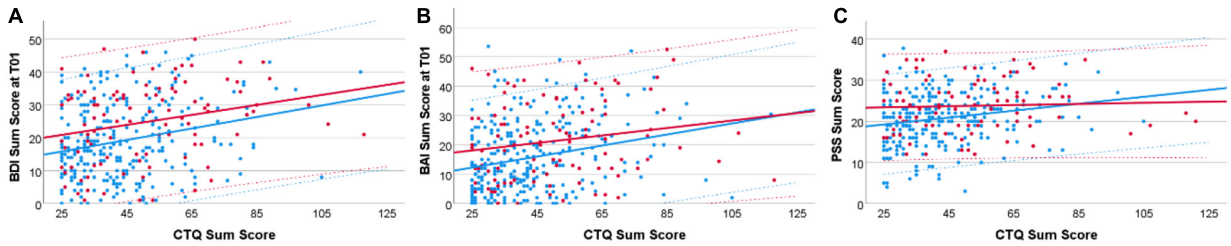

FIGURE 3 | Correlation between CTQ sum score and **(A)** depressiveness (BDI), **(B)** anxiety (BAI), and **(C)** perceived stress (PSS). In males (blue), a significant positive correlation was observed for all three clinical variables. In women (red), a significant positive correlation was observed only for depressiveness. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire; PSS, Perceived Stress Scale. Dotted lines indicate 95% confidence intervals.

prevalence rates for abuse but not neglect. Also, individuals with SUD suffered from significantly more severe experiences of CM for all subscales compared to the general German population (22). Our findings are consistent with previous studies, reporting a high prevalence and strong severity of CM in individuals with SUD (12, 15, 23, 58). Compared to a previous study on the severity of CM in individuals with SUD (23), we observed significantly less severe experiences of all forms of abuse but a more severe experience of physical neglect. A higher percentage of women in the previously reported SUD sample (41.3 vs. 27%) might contribute to these differences, since women are known to report higher severities of CM, which was also observed in our sample regarding emotional and sexual abuse. Also, Wingenfeld et al. (23) did not report on different substances. Depending on the composition of SUDs, group differences as we observed here might also contribute to the diverging observations.

Contrary to our hypothesis, individuals with OUD were not the most severely affected substance user group by CM in comparison to other SUD – although prevalence rates of OUD were comparable to previous studies (15, 58). This opposes previous research showing that individuals with OUD were more likely to report ACE in comparison to individuals with tobacco or cocaine use disorder (59). Others observed similar prevalence numbers of CM in both, individuals with OUD and matched controls, which was explained by the control group also containing individuals with other SUD. Still, males with OUD experienced significantly more physical and emotional abuse than controls, and females sexual abuse, respectively (60).

In our sample, patients with CUD showed both higher prevalence and more severe experiences of several subtypes of CM. Emotional abuse was significantly more severe in CUD compared to AUD. However, CUD compared to OUD did not reach significance. Individuals with CUD were similarly affected by comorbid mental disorders, i.e., schizophrenia, schizotypal and delusional disorders (F2), affective (F3), or neurotic, stress-related and somatoform disorders (F4) as AUD. *Post hoc* analyses (see **Supplementary Material**) for CUD and AUD did not yield significant group differences. However, individuals with CUD were diagnosed with more comorbid SUD compared to individuals with AUD. An explanation for our observation with respect to individuals with OUD might be three-fold. Firstly, an age effect cannot be ruled out regarding patients with CUD, since they were significantly younger. *Post hoc* analyses (see **Supplementary Material**) revealed a negative correlation between age and overall CM severity. However, within each substance group, including CUD, this correlation did not reach significance. Discussing generational aspect when it comes to (not) reporting CM are relevant, but beyond the scope of this retrospective, observational study. Secondly, CM data for OUD mainly derived from OMT patients. In contrast to the other SUD patients of our study, OMT patients were not abstinent, but continuously treated with opioids. Therefore the daily opioid treatment may have an acute effect and memories of CM might be suppressed to a certain extent. This could have led to an underreporting of prevalence and severity of CM. Opposing to this and besides psychobiological mechanism of withdrawal, in-house patients might find themselves strongly confronted with current problematic psychosocial factors during our treatment. They might increase attention toward traumatic events as one potential factor within the biopsychosocial model of addiction that is regularly discussed during medical and psychotherapeutic treatment of SUD. Thirdly, endocannabinoids mediate the extinction of aversive memories and regulate fear, anxiety and stress. External cannabis might enhance these effects, and thus might be consumed as a self-medication (61, 62). A systematic review of cannabis use motives identified negative life events, trauma, and maladaptive coping being related to consumption (63). This was also confirmed for CM as origin of negative stress and influenced by impairments in emotion regulation, e.g., negative mood (64). Cannabinoids are discussed as medical intervention for several anxiety- and trauma-related disorders by reason of their neuromodulator capacities in brain regions relevant for emotion and stress regulation (65, 66). Further research examined the hypothesis of a self-medication model of cannabis in posttraumatic stress disorder and revealed an acute, dose-dependent cannabis effect of a 51–67% symptom relief in more than 92% of cannabis users. However, a development of tolerance and therefore limited effects were observed (67).

Named considerations evoke the question of a causal origin of the association, namely whether CM is more frequent in SUD compared to the general population, because CM leads to SUD. Our analyses highlighted association between CM and SUD rather than causation. However, mechanisms identified in basic and animal research include a long lasting altered stress response after early life adversity. Further, perturbation of numerous neurodevelopmental processes, including the development and

maturation of brain circuits involved in cognition and emotion, finally result in diminished cognitive control and increased desire for drug effects, i.e., memory extinction and relief from negative affect. Mechanisms are reviewed in Al'absi et al. (68) and Levis et al. (69). Recent basic research supported the contribution of CM to an increase in vulnerability for opioid addiction (Sophia C. (70)), possibly mediated by the endogenous opioid system which is involved in pro-social behavior in mammals, including humans (71). A recent review proposes "[. . .] based upon recent findings of opioid modulation of human social learning, bonding and empathy in relation to affiliative and protective tendencies. Fundamental to the model is that the mu-opioid system reinforces socially affiliative or protective behavior in response to positive and negative social experiences with long-term consequences for social behavior and health" (72). Lacking of pro-social touch, caring and protective behavior in childhood is a key feature of CM and may result in a long-term modification of the endogenous opioid system. On the emotional level this might result in an enhanced desire for social attachment and the pro-social effects of endogenous or external opioids. Not only opioids but all addictive substances share an activation of the opioid system, either by releasing endogenous opioids (alcohol, cannabis, amphetamines, and cocaine) or by direct activation of opioid receptors (heroin and synthetic opioids) (73–76). Therefore, this opioid pathway also increases the risk for non-opioid SUD in individuals having experienced CM.

In our sample, a positive relation between the severity of the overall CM and depressiveness, anxiety and perceived stress was observed for males. However, in women, current perceived stress did not relate to a history of CM. The relation between ACE such as CM and a later SUD has been observed to be party mediated by mood and anxiety disorders (33).

The influence of sex with regard to outcomes of CM has been discussed previously (77) and sex differences are commonly accepted. However, White and Kaffman (77) argued that despite similar presentation, underlying mechanisms might differ. Also, impairments in mental health following CM are subject to effects of gender and CM subtype (78). Potentially, physical abuse is more often related to internalizing mental disorders (e.g., affective disorders) in females subjects whereas in males physical abuse more often related to externalizing mental disorders (e.g., SUD) (79). For women, but not men, several subtypes of CM were associated with an increased risk for cocaine relapse (80). In cocaine, CM might increase the risk for relapses due to an increased appetitive anticipatory response to drug cues. Further, regulatory and control mechanism regarding stress- and cocaine-induces craving might be reduced following CM (81).

Substance craving refers to a multifaceted construct, including internal and external factors as well as corresponding interactions, that results in the desire or urge for consumption (82). Further, within the diagnosis of SUD, craving is listed as a relevant item (43). In our sample, substance craving at admission to treatment differed between sex and substance group and was influenced by emotional abuse, but not other types of CM. Higher craving at admission to SUD treatment was previously related to relapse, i.e., in individuals with AUD (35, 83), indicating the importance of monitoring craving and examining influencing factors. Regarding a diverging influence of specific subtypes of CM, physical and emotional abuse, as well as emotional neglect were previously associated with drug use (84) and emotional abuse, followed by physical abuse, were the strongest predictors for the severity of AUD (31). However, depressiveness as a current affective state exerted a strong influence on craving at admission and on craving reduction over the course of treatment. The influence of anxiety on craving became apparent only at admission, whereas perceived stress significantly contributed to craving reduction. Within our sample, a positive correlations between CM and symptoms of depressiveness, anxiety, and perceived stress have been observed. Individuals with CM are at higher risk for psychopathologies related to anxiety and depressiveness (4). At the same time, symptoms of depressiveness and anxiety are common for individuals entering treatment for SUD and negatively influence treatment outcome, i.e., increased risk for relapse (85). In AUD, inefficient emotion regulation is associated with increased alcohol craving and use (86). A history of CM was related to alcohol craving as a response to traumatic stimuli in healthy males. Further, physiological markers, such as cortisol reactivity, heart rate or skin conductance were also related to alcohol craving, CM or both (87).

Limitations

Limitation, that might reduce the generalizability of the results have to be mentioned. First, possible limitations include the study being based on retrospective self-report questionnaires. Especially, when retrospectively assessing CM as it is done with the CTQ, answers might be biased. When assessing CM, a great heterogeneity regarding the instruments can be observed in the literature. Second, besides using questions defined by the authors, validated questionnaires, such as the CTQ, or interviews were used. When assessing ACE, CM has to be distinguished from a dysfunctional household (including divorce, substance use, observing intimate partner violence) *per se*. CM, abuse or neglect, account primarily for negative mental health outcomes in a study that examined individuals in their early and late adolescence (3). Due to the design of the here presented analyses, we did not assess other ACE besides CM as defined by CTQ and did not collect information about income or family structures which might have added to the biographical burden that possibly contributes to the development of SUD. This hinders the integration of study results in previous literature. Third, only patients were included in the analyses. Therefore, the influence of CM on the transition from low-risk to high-risk consumption possibly leading to a substance use disorder as well as characteristics inherent to non-treatment seeking individuals with SUD could not be examined. Fourth, substances were grouped and only the main diagnosis was considered. The small sample size for individuals with OUD or SHA does not allow for a broader discussion of the influence of main diagnosis on craving at admission and the reduction of craving during treatment.

Clinical Implications

The here observed high prevalence and severity of CM in individuals with CUD, but also recent developments in the pattern of consumption and the potency of the available

substances (88) underline the need for screening for CM both during treatment for CUD and in prevention of CUD. This is backed up by previous studies in individuals with both a history of CM and cannabis use that indicated a higher risk for psychotic symptoms in adolescents (89) and a more severe symptomatology for bipolar disorder (90). Irrespective of the substance of use, a high prevalence and severity of CM was underlining the importance of assessing CM with suitable tools in all settings of SUD prevention and treatment. If CM can be ceased and a positive environment is installed including intact social networks, positive coping, self-esteem and optimism, the neuro-adaptive capacities of the human brain might allow for a positive outcome, even following CM (91). For example, low levels of mindfulness might link CM to alcohol use (92), therefore serving as a therapeutic target. Individuals with SUD and CM might benefit from integrative psychosocial interventions targeting both, trauma-related and SUD-related symptoms (93), such as interpersonal psychotherapy (94) or trauma informed yoga (95, 96).

CONCLUSION

Individuals with SUD experience various forms of CM more often and in a more severe manner than the general population. SUD group differences with regard to prevalence and severity of CM were observed. Sex differences to the detriment of women can be observed in several SUDs. CM, specifically emotional abuse, might be related to craving at admission to treatment. However, pathways of mediating factors, such as depressiveness, anxiety and stress still have to be examined in more depth. Also, underlying causal and explanatory mechanism such as impairments in processing of trauma history, emotional regulation, or neurobiological alterations following CM remain to be further examined. A history of CM should be assessed during treatment for SUD. A possible positive influence of trauma-related interventions during SUD treatment specifically addressing aspects of CM on treatment outcomes and relapse rates can be hypothesized.

DATA AVAILABILITY STATEMENT

Data contains sensitive medical information and will be made available for researchers who meet the criteria for access to confidential data. The data underlying the results presented in the study are available upon reasonable request from SV-K (s.vollstaedt-klein@zi-mannheim.de).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (approval numbers 2018-531N-MA and 2018-807R-MA). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG designed the current study, performed the data analysis, and drafted the manuscript. KE and NB collected the parts of the data from study 2. SH supported the data analysis. KE, DH, AK, WS, and SV-K contributed to the interpretation of the data. KE helped with the writing of the manuscript. SV-K, FK, PB, NB, DH, AK, and WS were responsible for the study designs of the original studies and helped with the recruitment. DH, FK, and WS procured the funding of the original studies. All authors revised the manuscript critically for important intellectual content and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.866019/full#supplementary-material

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BRIEF RESEARCH REPORT
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Comorbid Affective and Substance Use Disorders of Medicaid/Medicare Beneficiaries at an Opioid Treatment Program Serving Small Urban and Rural Communities

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Objectives: Identify rates and correlates of comorbid affective and substance use disorders among an understudied population, Medicaid/Medicare beneficiaries receiving care at an opioid treatment program serving patients from small urban and rural areas. Examine whether past-year non-medical opioid use status differentiates comorbidity status.

Methods: A cross-sectional, venue-based design was used to recruit a convenience sample of patients treated with methadone for opioid use disorder. Measures were assessed across three domains: (1) demographic characteristics, (2) opioid use characteristics, and (3) comorbid disorders. Brief validated screeners categorized probable comorbid disorders. Bivariate analyses examined correlates of comorbid disorders and determined variable selection for multivariable analyses.

Results: In this sample (N = 210; mean age = 38.5 years; female = 62.2%; Non-Hispanic White race/ethnicity = 86.1%), comorbid disorders were common. Rates were as follows: current anxiety (48.1%), depression (41.1%), and PTSD (33.7%), and past-year stimulant (27.6%), marijuana (19.0%), alcohol (14.9%), and sedative (7.6%). In bivariate analyses, past-year non-medical opioid use and a greater accumulation of opioid use consequences were associated with most disorders. When including demographic and opioid use characteristics in multivariable analyses, past-year non-medical opioid use was associated with anxiety, PTSD, stimulant use disorder, and sedative use disorder.

Conclusions: Few studies have investigated comorbid disorders among this understudied population. This analysis highlights a high burden, especially for affective disorders. Our findings demonstrate that routine, ongoing assessment of non-medical

opioid use may be a promising and feasible strategy to detect patients needing integrated care. Future research should investigate whether changes to assessment protocols at opioid treatment programs in small urban and rural settings facilitate care coordination.

Keywords: comorbid, opioid use disorder, affective disorder, substance use disorder, methadone, Medicare and Medicaid, rural, urban

INTRODUCTION

People receiving methadone treatment for opioid use disorder (OUD) often have multiple morbidities. Studies estimate that more than 80% of patients in methadone treatment have at least one comorbid affective or substance use disorder (1, 2). Among people with OUD, past-year comorbidity rates range from 13 to 26% for alcohol, cannabis, cocaine, and sedative use disorder, and 64% have at least one mental health disorder (3). Comorbid disorders, especially other substance use disorders, are associated with worse treatment outcomes (1, 4). Comorbid depressive, trauma-related, and anxiety disorders, while less consistent risk factors for worse treatment outcomes (1, 5, 6), necessitate assessment and integrated approaches. These are especially urgent considering people with comorbid substance use and affective disorders are at high risk for fatal overdose people compared to those without comorbid disorders (7). While facilities providing methadone in the United States, formally called opioid treatment programs (OTPs), are required to provide substance use counseling or behavioral therapies in conjunction with medication treatment (8), there is no specific requirement for those counseling services to address co-occurring affective disorders (9).

Assessment and monitoring of methadone treatment processes and outcomes are required by federal guidelines for OTPs; and these guidelines recommend assessment of comorbid disorders (10). The Substance Abuse and Mental Health Services Administration (SAMHSA) advocates for the use of validated screening and assessment tools in their Treatment Improvement Protocol series on substance use and co-occurring disorders (11). However, because the use of validated tools is not a formal requirement for OTP intake, non-validated instruments developed by local and state treatment authorities are commonly used (12). Furthermore, some patients may not report psychiatric distress early in treatment (i.e., during intake assessment), but may experience symptoms that begin after induction or stabilization to methadone. Therefore, quickly screening patients at regular intervals throughout treatment may identify the need for integrated care approaches to address comorbid affective and substance use disorders. Furthermore, identifying innovative yet feasible strategies, such as low-burden screening, represents an approach that may improve care and be better adopted than resource-intensive strategies not well suited for the complexity of the existing addiction treatment system.

Screening for comorbid affective and substance use disorders in small urban and rural communities may be particularly important. People with comorbid disorders living in these settings often experience considerable challenges when trying to access care that is located outside of their OTP, due primarily to travel and transportation barriers, whether personal or public (13, 14). Research has demonstrated that OTP patients referred to care offsite are at risk for poor treatment attendance and retention (15, 16). Thus, the use of validated screening measures, which assess comorbid disorder symptoms and non-medical opioid use patterns during treatment, have the potential to improve co-located care coordination at OTPs serving small urban and rural patient populations, and address a largely unmet comorbid disorder burden.

To date, investigations gathering primary data on comorbid disorders among patients in methadone treatment are restricted mainly to samples from large urban areas, due to a scarcity of OTPs in small urban and rural areas (17, 18) and relatively few patients traveling to large urban areas from smaller surrounding communities (13). Furthermore, primary data studies of patients being treated with methadone rarely constrain the sample to target the needs of publicly-insured populations, despite disproportionate odds for methadone services to be paid by public funds (19), and higher odds of opioid overdose among Medicaid/Medicare beneficiaries (20).

This study represents the first primary data collection addressing comorbid affective and substance use disorders among a sample of Medicaid/Medicare beneficiary patients from small urban and rural communities receiving methadone treatment. Our aims were as follows. We sought to identify rates of probable comorbid affective and substance use disorders using validated screening tools; examine demographic and opioid use characteristic correlates of comorbid disorders; and investigate whether past-year non-medical opioid use status was a significant differentiator of comorbid disorder status in multivariable analyses when including other key characteristics. We hypothesized that a high rate of comorbid disorders would be observed, with stronger correlations for opioid use characteristic variables and comorbid disorders than for demographic characteristics and comorbid disorders. Last, we hypothesized that past-year non-medical opioid use status would be the most consistent correlate of comorbid disorders in multivariable analyses.

MATERIALS AND METHODS

Setting and Procedure

A venue-based recruitment strategy was used to recruit patients receiving methadone for OUD at an OTP situated in a medically underserved area of a small urban county (Rural Urban Continuum Code/RUCC = 3) (21). The clinic's catchment area extends to several surrounding rural counties (RUCCs = 4–7) (21) south of the clinic, and rural census tracts, using Federal

Office of Rural Health Policy definitions for rural zip codes in urban counties (22), situated north and west of the clinic.

Data collection occurred over 3 weeks in December 2019 (23), with 267 patients enrolled in the parent study. In the weeks before data collection, OTP staff informed patients of the study and distributed recruitment materials. Research staff were onsite for data collection three varied days of each week. A convenience sample of patients completed self-administered computer-based surveys in a private room located at the clinic. Research staff obtained informed consent (using an information sheet approved with a documentation waiver), assisted with surveys as needed (e.g., due to difficulties with reading or technology), and provided compensation ($25 gift card to a large shopping outlet) for completing surveys.

For this analysis, we focus on the subset of patients who had their treatment funded by Medicaid or Medicare. All patients were eligible for this analysis, regardless of when they started treatment. Thus, the sample includes patients new to treatment, as well as those who were engaged with the clinic for long-term care. We focus on the analytic sample of Medicaid/Medicare beneficiaries receiving methadone treatment[1] because preliminary analyses demonstrated higher rates of comorbid disorders among Medicaid/Medicare beneficiaries compared to patients reporting private health insurance or self-pay. This is consistent with literature showing a greater comorbidity burden among publicly-insured populations with OUD (24). Additionally, we were not adequately powered to compare differences based on payment type in the analytic sample ($N = 210$; Medicaid: $n = 196$, 93.3%; Medicare: $n = 14$, 6.7%). All study procedures were approved by the Wayne State University Institutional Review Board.

Measures

Surveys assessed measures across three domains: demographic characteristics, opioid use characteristics, and comorbid affective and substance use disorder screening measures.

Demographic Characteristics

Patients provided demographic information, including their current age (years), geography (zip code of residence), gender identity (male, female, other), race/ethnicity (Arabic/Middle Eastern, Hispanic/Latino, Non-Hispanic African American, Non-Hispanic Asian, Non-Hispanic Native American, Non-Hispanic Native Hawaiian, Non-Hispanic White, Non-Hispanic more than one race), educational attainment (earned high school diploma or GED, had not earned a high school diploma or GED), and their public health insurance type (Medicaid, Medicare). To measure rural-urban community of residence, we used the Goldsmith Modification (25), a technique outlined by the Federal Office of Rural Health Policy to categorize rurality using patient zip codes at the county (RUCCs 4–9) and federally-defined rural census tracts (i.e., rural zip codes embedded within urban counties). Though the gender item included a non-binary response option, no patients reported a gender aside from male or female. Because the sample was predominantly Non-Hispanic White and other race/ethnicity groups were smaller (<5%), race/ethnicity was dichotomized (Non-Hispanic White, other race/ethnicity) to ensure adequate statistical power to detect group differences.

Opioid Use Characteristics

Patients answered questions about five opioid use characteristics. These brief measures were selected due to high clinical feasibility and reduced patient burden. First, patients were asked about non-medical opioid use in the past year. Past-year non-medical opioid use was then compared with the date the patient started their current treatment episode to indicate the absence of past-year use (reference category) or occurrence of past-year use before starting treatment or while in treatment (coded as 1 and 2). Patients reported their history of fentanyl use, whether intentional or unintentional (dichotomous: no history, history), as well as their preference for injection drug use (dichotomous: not preferred, preferred). Patients also completed an adapted version of the Heroin Use Consequence scale (26) to assess lifetime opioid use consequences. Though the original HUC scale focuses on consequences of heroin use specifically, in the current study patients were asked to consider their use of all opioids except those used as directed by a doctor. Education-related consequences (three items from the original 20-item scale), that were among the least endorsed in the scale development study (26), were excluded to reduce time burden. This resulted in a total of 17 items that were summed. Last, we assessed whether patients had been in treatment during the current episode for 1 year or more.

Comorbid Affective and Substance Use Disorder Screening Measures

Validated screens were administered for seven comorbid disorders. Established cut scores were used to categorize patients as having probable comorbid disorders (i.e., positive screens). Three screens assessed probable comorbid affective disorders, including depression (Patient Health Questionaire-2; PHQ-2, a score of three or greater during the past 2 weeks was interpreted as a positive screen) (27), anxiety (Generalized Anxiety Disorder 2-Item Scale; GAD-2, a score of three or greater during the past 2 weeks was interpreted as a positive screen) (27), and PTSD (Primary Care PTSD Screen for DSM-5; PC-PTSD-5, a score of four or greater during the past month was interpreted as a positive screen) (28). Four screens assessed probable comorbid substance use disorders during the past year, including stimulants (Stimulant Severity of Dependence Scale, a score of three or greater was used) (29), cannabis (Cannabis Severity of Dependence scale, a score of three or greater was used) (30), alcohol (AUDIT-C, for women, a score of three or greater was used and for men a score of four or greater was used to identify patients with hazardous drinking or active alcohol use disorder) (31), and sedatives (Sedative Severity of Dependence Scale, a score of six or greater was used) (29).

[1] Forty cases were excluded when treatment was funded by private health insurance ($n = 34$) or self-pay ($n = 6$). An additional 17 cases were removed for missing data on key study variables (past-year non-medical opioid use, current methadone status).

Data Analysis

We analyzed data using SPSS version 27 (IBM Corp., 2017). After the removal of patients from the analytic sample (described in Settings and Procedure), cases from variables with small amounts of missing data (1–2 cases) were removed using listwise deletion by default. Little's MCAR test indicated data were missing completely at random [$\chi 2$ (158) = 169.586, $p = 0.250$] (32). Measures of central tendency and distribution were calculated for all variables. Group (*t*-tests, chi-square, one-way ANOVA) and correlation analyses (Kendall's Tau-b) explored differences and associations between demographic characteristics, opioid use characteristics, and comorbid disorder screening measures. Adjusted standardized residuals (ASRs) were used to estimate low ($\leq$-2) and high values ($\geq$2), in line with Haberman's rule of thumb (33), in bivariate analyses of past-year non-medical opioid use status (a three-level categorical variable). We then conducted binomial logistic regressions to examine whether past-year non-medical opioid use status remained a significant differentiator of probable comorbid disorders after including demographic and opioid use characteristics that demonstrated directional ($p < 0.20$) associations in bivariate analyses. Since the comorbid disorder screening measures for alcohol and depression did not differ by past-year non-medical opioid use status in bivariate analyses, they were not included alongside the other five comorbid disorder screening measures as dependent variables in multivariable regression analyses. Due to collinearity with past-year non-medical opioid misuse status, time in treatment was excluded from multivariable analyses.

TABLE 1 | Sample characteristics ($N = 210$).

	n	Valid %	*M* (SD)
Demographic characteristics			
Age (in years)			38.53 (10.13)
Female gender	130	62.2	
High school degree or equivalent	158	75.2	
Non-Hispanic White race/ethnicity	180	86.1	
Rural community	29	14.4	
Opioid use characteristics			
Fentanyl use	129	61.7	
Injection preference	83	39.5	
Opioid use consequences			10.25 (4.49)
Time in treatment > 1 year	169	71.6	
Comorbid disorders			
Depression	85	41.1	
Anxiety	100	48.1	
PTSD	70	33.7	
Alcohol	31	14.9	
Marijuana	40	19.0	
Stimulant	58	27.6	
Sedative	16	7.6	

Age range, 22–72 years. Frequencies for other race/ethnicity groups: Non-Hispanic more than one race (n = 10, 4.8%), Non-Hispanic African American or Black (n = 8, 3.8%), Hispanic any race (n = 7, 3.3%), Non-Hispanic Asian American (n = 2, 1/0%), and Non-Hispanic Native American or Alaska Native (n = 2, 1.0%). Reference groups (in parentheses) were as follows: gender (male), education (less than HS/GED), race (other race/ethnicity), community (non-rural), fentanyl use (no history), and injection opioid use (no history).

RESULTS

Sample Description

Table 1 displays descriptive information about the analytic sample for demographic characteristics, opioid use characteristics, and rates of comorbid disorders.

Group Differences for Comorbid Disorders by Demographic and Opioid Use Characteristics

Table 2 presents bivariate relationships between demographic and opioid use characteristics and each of the seven comorbid disorder screening measures. Younger age was associated with PTSD ($p < 0.001$), and lower educational attainment was associated with sedative use disorder ($p < 0.05$). Other demographic characteristics met bivariate determination ($p < 0.20$) for multivariable regression analyses, including the negative relationships between female gender and marijuana use disorder and the positive relationship between female gender and anxiety and alcohol use disorder, and the positive relationship between living in a rural community and marijuana use disorder. The Non-Hispanic White race/ethnicity variable was excluded from the sedative use disorder model in bivariate and multivariable analyses due to perfect separation (i.e., 100% of the patients with sedative use disorder reported non-Hispanic White race/ethnicity).

With regard to opioid use characteristics, a greater lifetime accumulation of opioid use consequences was positively associated with PTSD ($p < 0.001$), stimulant use disorder ($p < 0.001$), anxiety ($p < 0.01$), sedative use disorder ($p < 0.01$), and met bivariate determination ($p < 0.20$) for marijuana use disorder and depression. A history of fentanyl use was associated with PTSD ($p < 0.01$), sedative use disorder ($p < 0.05$), and stimulant use disorder ($p < 0.05$). A preference for injection drug use was unrelated to all comorbid disorder screens, but did meet bivariate determination ($p < 0.20$) for sedative use disorder.

Group Differences for Comorbid Disorders by Past-Year Non-Medical Opioid Use Status

Table 3 displays bivariate analyses for comorbid disorder screening measures by past-year non-medical opioid use status. Five of the seven comorbid disorders, including anxiety ($p < 0.05$), PTSD ($p < 0.001$), marijuana use disorder ($p < 0.05$), stimulant use disorder ($p < 0.001$), and sedative use disorder ($p < 0.01$) differed significantly by past-year non-medical opioid use status, whereas depression and alcohol use disorder were unrelated. High and/or low ASR values were examined for the same five comorbid disorders among the three past-year non-medical opioid use status groups. Specifically, patients reporting no past-year non-medical opioid use had low levels (ASR $\leq$-2) of anxiety, PTSD, marijuana use disorder, stimulant use disorder, and sedative use disorder. In contrast, patients reporting past-year non-medical opioid use that occurred before treatment had

TABLE 2 | Group differences for comorbid disorders by demographic and opioid use characteristics.

	Depression	Anxiety	PTSD	Alcohol	Marijuana	Stimulant	Sedative
Demographic characteristics							
Age	$\tau_b = -0.004$	$\tau_b = -0.050$	$\tau_b = -0.217$	$\tau_b = 0.016$	$\tau_b = -0.014$	$\tau_b = 0.024$	$\tau_b = -0.043$
	$p = 0.951$	$p = 0.386$	$p = 0.000$	$p = 0.791$	$p = 0.808$	$p = 0.682$	$p = 0.455$
Female gender	$t = 0.234$	$t = 1.479$	$t = 0.818$	$t = 1.423$	$t = -1.561$	$t = -0.145$	$t = 0.002$
	$p = 0.815$	$p = 0.141$	$p = 0.414$	$p = 0.156$	$p = 0.120$	$p = 0.885$	$p = 0.980$
High school degree or equivalent	$t = -0.672$	$t = -1.121$	$t = 0.735$	$t = -0.703$	$t = -1.259$	$t = -0.227$	$t = -0.168$
	$p = 0.502$	$p = 0.264$	$p = 0.463$	$p = 0.483$	$p = 0.209$	$p = 0.821$	$p = 0.015$
Non-Hispanic White race/ethnicity	$t = -0.014$	$t = 1.025$	$t = -0.227$	$t = -0.927$	$t = -0.228$	$t = 0.407$	*excluded from the model*[a]
	$p = 0.989$	$p = 0.306$	$p = 0.820$	$p = 0.355$	$p = 0.820$	$p = 0.685$	
Rural community	$t = -0.268$	$t = -0.711$	$t = 0.481$	$t = -0.184$	$t = 1.707$	$t = -0.402$	$t = 0.046$
	$p = 0.789$	$p = 0.478$	$p = 0.631$	$p = 0.854$	$p = 0.191$	$p = 0.688$	$p = 0.519$
Opioid use characteristics							
Fentanyl use	$t = 0.234$	$t = 1.794$	$t = 2.769$	$t = 0.391$	$t = 1.067$	$t = 2.193$	$t = 0.153$
	$p = 0.815$	$p = 0.074$	$p = 0.006$	$p = 0.697$	$p = 0.287$	$p = 0.029$	$p = 0.028$
Injection preference	$t = 1.127$	$t = 0.592$	$t = -0.178$	$t = 1.167$	$t = -0.290$	$t = 0.338$	$t = 0.098$
	$p = 0.261$	$p = 0.555$	$p = 0.859$	$p = 0.244$	$p = 0.772$	$p = 0.736$	$p = 0.155$
Opioid use consequences	$\tau_b = 0.079$	$\tau_b = 0.173$	$\tau_b = 0.254$	$\tau_b = -0.028$	$\tau_b = 0.094$	$\tau_b = 0.229$	$\tau_b = 0.170$
	$p = 0.178$	$p = 0.002$	$p = 0.000$	$p = 0.605$	$p = 0.121$	$p = 0.000$	$p = 0.004$

Bivariate analyses use Kendall's tau-b (τ_b) and t-tests. Listwise n = 200. Alpha threshold ($p < 0.20$, two-tailed) used for bivariate determination procedures in multivariable models. Reference groups (in parentheses) were as follows: gender (male), education (less than HS/GED), race (other race/ethnicity), community (non-rural), fentanyl use (no history), and injection opioid use (no history).

[a]*Race/ethnicity variable was excluded from the sedative use disorder model analysis due to perfect separation (100% of patients with sedative use disorder reported Non-Hispanic White race/ethnicity).*

high levels (ASR ≥2) of PTSD, marijuana use disorder, and stimulant use disorder, while patients reporting past-year non-medical opioid use while in treatment had high levels (ASR ≥2) of stimulant use disorder and sedative disorder.

Multivariable Regressions of Comorbid Disorders

Five separate multivariable regression models were conducted (see **Table 4**). Four models were significant (PTSD: $p < 0.001$; stimulant use disorder: $p < 0.001$; sedative use disorder: $p < 0.001$; anxiety: $p < 0.01$), and one was not (marijuana use disorder: $p > 0.05$).

Past-year non-medical opioid use before treatment was significant in three models (PTSD: $p < 0.01$; stimulant: $p < 0.01$; sedative: $p < 0.05$). Past-year non-medical opioid use while in treatment was significant in two models (stimulant: $p < 0.001$; sedative: $p < 0.05$). A greater number of opioid use consequences was significant in two models (PTSD: $p < 0.01$; stimulant: $p < 0.05$). Other significant variables included younger age in the PTSD model ($p < 0.01$), lower educational attainment in the sedative model ($p < .05$), and female gender in the anxiety model ($p < 0.05$). Fentanyl use, injection drug use preference, Non-Hispanic White race/ethnicity, and rural community were not significant in any models.

DISCUSSION

This study identified rates and correlates of comorbid disorders among Medicaid/Medicare beneficiary patients from small urban and rural communities receiving methadone treatment for OUD. This analysis highlights a high comorbidity burden, especially for affective disorders. Our findings also reveal a consistent role for past-year non-medical opioid use to detect patients in greater need of integrated care for comorbid disorders. To date, few studies have examined comorbid affective and substance use disorders among this understudied population.

Comorbid disorders were common in this sample, especially for affective disorders, with rates of 48, 41, and 34%, for anxiety, depression, and PTSD, respectively. Consistent with predictions, rates were lower for comorbid substance use disorders, though 28% of patients still screened positive for stimulant use disorder. When analyzing differences by past-year non-medical opioid use status, considerably higher rates for all seven comorbid disorders were demonstrated among patients reporting use before and/or while in treatment. As illustration, within the sub-sample of patients reporting past-year use that occurred before treatment, or while in treatment, 62 and 57%, respectively, screened positive for anxiety, compared to 39% of patients reporting no past-year use. Similarly, 62% of patients reporting past-year use while in treatment screened positive for PTSD, compared to 39% reporting past-year before treatment, and 23% reporting no past-year use. The difference was starkest for stimulant use disorder, where 46% (past-year use while in treatment) and 45% (past-year use before treatment), respectively, screened positive, compared to only 12% of patients reporting no past-year use. For all seven disorders assessed, patients reporting no past-year use had lower rates than either group reporting past-year use, regardless of whether it occurred before or while in treatment. Consistent with hypotheses, these relationships remained even when accounting

TABLE 3 | Group differences for comorbid disorders by past-year non-medical opioid use status.

	Depression	Anxiety	PTSD	Alcohol	Marijuana	Stimulant	Sedative
No PY non-medical opioid use ($n = 113$)	37.3 (41)	38.9 (43)[a]	23.2 (26)[a]	10.8 (12)	12.4 (14)[a]	12.4 (14)[a]	1.8 (2)[a]
PY non-medical opioid use, before tx ($n = 29$)	44.8 (13)	62.1 (18)	62.1 (18)[b]	20.7 (6)	34.5 (10)[b]	44.8 (13)[b]	13.8 (4)
PY non-medical opioid use, while in tx ($n = 68$)	45.6 (31)	57.4 (39)	38.8 (26)	19.1 (13)	23.5 (16)	45.6 (31) [b]	14.7 (10)[b]
Total sample	41.1 (85)	48.1 (100)	33.7 (70)	14.9 (31)	19.0 (40)	27.6 (58)	7.6 (16)
	$\chi^2 = 1.398$, $p = 0.497$	$\chi^2 = 8.496$, $p = 0.014$	$\chi^2 = 16.75$ $p<0.001$	$\chi^2 = 3.184$, $p = 0.204$	$\chi^2 = 8.615$, $p = 0.013$	$\chi^2 = 28.390$, $p<0.001$	$\chi^2 = 11.915$, $p = 0.003$

PY, past-year; tx, treatment. All values reported are "valid % (n)" unless otherwise noted.
[a]Adjusted Standardized Residual (ASR) = ≤-2.
[b]Adjusted Standardized Residual (ASR) = ≥2.

TABLE 4 | Multivariable regressions of comorbid disorders.

Variable	Anxiety	PTSD	Marijuana	Stimulant	Sedative
PY non-medical opioid use, before tx	$B = 0.737$, $p = 0.113$ 95% CI = 0.84−5.20	$B = 1.478$, $p = 0.003$** 95% CI = 1.67−11.52	$B = 1.024$, $p = 0.056$ 95% CI = 0.97−7.96	$B = 1.373$, $p = 0.006$** 95% CI = 1.50−10.42	$B = 1.912$, $p = 0.042$* 95% CI = 1.07−42.75
PY non-medical opioid use, while in tx	$B = 0.603$, $p = 0.072$ 95% CI = 0.95−3.53	$B = 0.372$, $p = 0.314$ 95% CI = 0.70−2.99	$B = 0.588$, $p = 0.169$ 95% CI = 0.78−4.17	$B = 1.572$, $p<.001$*** 95% CI = 2.24−10.38	$B = 2.116$, $p = 0.012$* 95% CI = 1.61−42.88
Age	Not in model	$B = -0.059$, $p = 0.003$** 95% CI = 0.91−0.98	Not in model	Not in model	Not in model
Female gender identity	$B = 0.644$, $p = 0.038$* 95% CI = 1.04−3.50	Not in model	$B = -0.455$, $p = 0.634$ 95% CI = 0.30−1.33	Not in model	Not in model
High school degree or equivalent	Not in model	Not in model	Not in model	Not in model	$B = -1.458$, $p = 0.012$* 95% CI = 0.07−0.73
Non-Hispanic White race/ethnicity	Not in model	Not in model	Not in model	Not in model	Excluded from analysis[a]
Rural community	Not in model	Not in model	$B = 0.608$, $p = 0.478$ 95% CI = 0.72−4.69	Not in model	Not in model
Fentanyl use	$B = 0.209$, $p = 0.541$ 95% CI = 0.63−2.41	$B = 0.121$, $p = 0.753$ 95% CI = 0.53−2.40	Not in model	$B = -0.019$, $p = 0.963$ 95% CI = 0.45−2.16	$B = 0.544$, $p = 0.525$ 95% CI = 0.32−9.25
Injection preference	Not in model	Not in model	Not in model	Not in model	$B = -0.147$, $p = 0.801$ 95% CI = 0.37−3.64
Opioid use consequences	$B = 0.067$, $p = 0.074$ 95% CI = 0.99−1.15	$B = 0.112$, $p = 0.009$** 95% CI = 1.03−1.22	$B = 0.020$, $p = 0.663$ 95% CI = 0.93−1.12	$B = 0.110$, $p = 0.019$* 95% CI = 1.02−0.23	$B = 0.146$, $p = 0.111$ 95% CI = 0.97−1.39
Model metrics	$\chi^2(5) = 16.931$ $R^2 = 0.105$, $p = 0.005$	$\chi^2(5) = 39.991$ $R^2 = 0.243$, $p<.001$	$\chi^2(5) = 8.736$ $R^2 = 0.069$, $p = 0.120$	$\chi^2(4) = 34.324$ $R^2 = 0.222$, $p<.001$	$\chi^2(6) = 25.126$ $R^2 = 0.271$, $p<.001$

**p < 0.05.*
***p < 0.01.*
****p < 0.001.*
PY, past-year; tx, treatment. Variables not in model did meet alpha threshold (p < 0.20, two-tailed) in bivariate analyses of comorbid psychiatric disorders. No PY non-medical opioid use was the reference group for PY non-medical opioid use, before tx and PY non-medical opioid use, while in tx.
[a]Race/ethnicity variable was excluded from the sedative use disorder model analysis due to perfect separation (100% of patients with sedative use disorder reported Non-Hispanic White race/ethnicity). All R^2 were Nagelkerke R Square values.

for other demographic and opioid use characteristics, as past-year non-medical opioid use was the variable most consistently associated with comorbid disorders in multivariable analyses. This relationship was strongest for PTSD, stimulant use disorder, and sedative use disorder.

One other opioid use characteristic, opioid use consequences, was associated with an increased likelihood of having comorbid disorders. In bivariate analyses, a greater number of consequences was associated with higher rates for anxiety, PTSD, stimulant use disorder, and sedative use disorder, though in multivariable analyses, significant associations only remained for PTSD and stimulant use disorder. This finding extends prior work demonstrating that a greater accumulation of opioid use consequences increases the likelihood of comorbid affective

disorder symptoms among people who regularly use heroin in a large urban area in the same state as this study (34). Injection use preference was not related to comorbid disorder status, despite prior research demonstrating an association between injection use and comorbid affective and substance use disorders among participants in large urban areas (35, 36). Similarly, fentanyl use was not related to comorbid disorders. Our analysis may highlight that even though fentanyl penetration to the drug supply and comorbidity are key contributors to overdose risk among Medicaid beneficiaries (37), in this geographic setting, the relationship of fentanyl use and comorbidity may be better understood as an interactive (vs. probabilistic) relationship. With regard to demographic characteristics, few relationships were observed. Younger age, lower educational attainment, and female gender were associated with a greater likelihood of PTSD, stimulant use disorder, and anxiety, respectively. Comorbid disorder status was unrelated to race/ethnicity in this sample. Similarly, rates did not differ for patients from rural areas compared to those residing in the small urban area where the OTP is located, suggesting that comorbid disorders among rural and small urban patients may be more similar than different.

The findings from this study highlight a few clinical implications. First, we suggest treatment authorities require OTPs to use validated screening tools for comorbid disorders, going a step further than current federal guidelines (9, 10). Second, we recommend that capacity and planning for coordinated care, particularly for affective disorders, be built into existing intake procedures. These strategies might include providing co-located services for affective disorders (15), developing partnerships for mental health service provision that build in accommodations for people living in small urban and rural areas (38), or evaluating the efficacy of evidence-based approaches for affective disorders, such as the Unified Protocol or Acceptance and Commitment Therapy (39, 40), when implemented through telehealth or adapted as computer-delivered interventions. Regardless of the strategy to assess and coordinate care, approaches should emphasize feasible innovations that mitigate implementation barriers and present financially sustainable changes at OTPs to facilitate adoption in a complex treatment system. The use of mixed methods implementation science protocols, such as NIATx (41), adapted to OTP settings in small urban and rural settings, may be a promising strategy to identify a more comprehensive understanding of patient and provider experiences as a means of improving and sustaining innovations to existing care models. This may be especially important at treatment intake, given that nearly all patients (e.g., transfers excluded), initiate methadone treatment following recent and ongoing non-medical opioid use, a robust correlate of affective disorder comorbidity in this sample. Third, we recommend future research that examines whether routinely screening patients (e.g., during clinical sessions and/or through short message services) engaged in long-term treatment for recent non-medical opioid use is feasible and improves linkage to care for comorbid disorders. Findings may provide support for the one-item measure presented here as a more efficient and less invasive method than current protocols (e.g., urine drug screens). Last, polysubstance use of stimulants and opioids has been rising nationally, and is a key determinant in the fourth wave of the opioid overdose crisis (42). While this study didn't directly assess polysubstance use, the high rates of comorbid stimulant use disorder in this sample of OUD patients suggests polysubstance use is occurring for a sizable portion of patients, who urgently need integrated approaches that can reduce overdose-related harm.

This study has limitations. First, the sample was a convenience sample with a heterogeneous length of care for their current treatment episode. While this does introduce important differences, many studies examine recent non-medical opioid use without inquiring about treatment engagement. Furthermore, we sought to counteract this heterogeneity and aid clinical interpretation by providing comorbid disorder rates within sub-samples categorized by past-year non-medical opioid use status. Second, we did not assess all possible comorbid affective and substance use disorders, in part due to time constraints to gather info on disorders with low base rates (e.g., schizophrenia, hallucinogen use disorder). Similarly, we did not assess addictions not commonly addressed at OTPs (e.g., tobacco use disorder, gambling disorder), nor did we assess comorbid health conditions, such as infectious diseases, that overlap with OUD (43), and represent other important avenues where integrated approaches improve treatment outcomes (44). Future studies should investigate a full spectrum of OUD-related comorbidities, which ostensibly would highlight an even higher comorbidity burden and need for integrated approaches than this analysis. Third, our sample, while innovative in many ways (small urban and rural setting, public insurance homogeneity), was not powered to conduct an in-depth comparison of racial differences or population-specific comorbidity patterns (e.g., comorbid disorder rates among Black/African American patients), which may have provided valuable information about health disparities. Future research should gather data in small urban and/or rural settings where there is a greater representation of Medicaid/Medicare beneficiaries from diverse racial groups (e.g., Black/African Americans in the Deep South, Hispanic/Latinos in the American Southwest, and Native Americans in the Great Plains) who are receiving methadone treatment. Last, our comorbid affective disorder screening measures, while using established administration instructions and timelines, did not assess whether the patient would've screened positive at other time points in the past-year. As a result, our analysis may underestimate the rates of affective disorders compared to other studies (3, 45).

In conclusion, this study highlights a high rate of comorbid disorders, especially affective disorders, among publicly-insured methadone patients from small urban and rural areas. This burden is especially high for patients reporting recent non-medical opioid use, regardless of whether that use occurred before or during their current methadone treatment episode. Innovative and feasible approaches that assess patients for comorbid disorders and recent non-medical opioid use are needed to improve care coordination. We encourage local and federal treatment authorities, OTP directors, and methadone treatment researchers to consider our findings when developing screening, implementation, and coordinated care strategies.

DATA AVAILABILITY STATEMENT

The dataset presented in this article are not readily available because participants of this study did not agree for their data to be shared publicly, so supporting data is not available. Requests to access the dataset should be directed to JL (jlister@ssw.rutgers.edu), SR (stella@wayne.edu), and EA (ad2634@wayne.edu).

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by the Wayne State University Institutional Review Board. Participants read an information sheet prior to participating in this study. Written informed consent was not required, as a waiver of documentation was obtained.

AUTHOR CONTRIBUTIONS

JL, GL, JE, EP, EA, and SR: led writing, conceptualization, and methodology. JL and JE: oversaw data analyses. GL: led data analyses. EA and SR: provided reviews. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Sex Specific Sleep Parameters Among People With Substance Use Disorder

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Introduction: Sleep can have substantial impacts in substance use disorder (SUD) pathogenesis, treatment, and recovery. Sex differences exist in both sleep and SUD, but how sleep is uniquely associated with SUD by sex is not known. The study objective was to compare, within sex, sleep parameters between individuals with SUD and non-substance misusing controls.

Methods: Secondary analyses of a parent cross-sectional study examining the feasibility and acceptability of a novel neurocognitive phenotyping assessment battery were completed. SUD and control subjects were recruited through local advertising and an established research registry. Subjects with SUD were also recruited through a university-based outpatient SUD treatment clinic. Self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). Sex-stratified *t*-tests compared sleep between SUD and control subjects while Crosstab analyses explored group differences in the proportion of individuals reporting poor sleep (defined as PSQI $\geq$ 5).

Results: Data from 162 males (44 controls, 118 SUD) and 146 females (64 controls, 82 SUD) were included in the present study. For females only, a significantly lower proportion of controls reported PSQI-defined poor sleep than individuals with any SUD or specifically with opioid use disorder. Male, but not female, controls reported shorter sleep latency, longer sleep duration, and less sleep disturbance than males with each SUD type.

Discussion/Implications: Sleep holds promise as an avenue to address SUD within a biopsychosocial model. Future work at the intersection of SUD and sleep should prioritize investigations of their interplay with sex to identify targets for tailored SUD interventions.

Keywords: addiction, substance use disorder, opioid use disorder, sleep, cannabis use disorder, cocaine use disorder, sex differences

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INTRODUCTION

Deaths due to substance use disorder (SUD) occur more often in males than females, yet increases in SUD-related mortality are occurring more rapidly for females than males (1). Females with opioid use disorder (OUD) are witnessing faster increases in overdose rates due to fentanyl than males (2). Stimulant use has skyrocketed as a cause of death (3), with females burdening additional negative impacts (4, 5).

Sex differences exist in SUD risk (6, 7) and treatment (8, 9). Examples include females progressing more rapidly from initial use to SUD (10) and males receiving buprenorphine having worse OUD treatment continuation rates (11). Given these sex differences, achieving a deeper understanding of the role that sex, as a key biological variable, plays in SUD is warranted.

New, effective SUD treatment options tailored to individuals' neurobiological characteristics and social contexts are urgently needed (12). One area receiving increased attention as a target for SUD prevention, assessment, treatment and recovery is sleep (13). Sleep and SUD demonstrate a bi-directional relationship (14, 15), and this intersection likely brings complexity to SUD trajectories. Specifically, substance use itself can negatively impact sleep quality (16–18). Simultaneously, sleep health may heighten or buffer risk for SUD development (19) and treatment response (20–22). In the general population, sex differences exist across sleep parameters (23), with sleep disturbance generally being more common among females than males (24).

Prior efforts attempting to assess sex-specific associations between sleep and SUD have been limited and inconclusive (25). The present study's primary objective was to compare, within sex, sleep parameters between individuals with SUD and non-substance misusing controls. The secondary objective was to report sex-specific differences in sleep parameters by primary drug diagnosis between SUD and control subjects. We hypothesized that poor sleep parameters would be more prevalent among the SUD groups than controls for both sexes.

MATERIALS AND METHODS

The Virginia Commonwealth University IRB (IRB# HM 20012559) approved the study, and written informed consent was obtained.

Subjects and Study Procedures

Methods for the parent study are described elsewhere (26). The objective of the parent, cross-sectional study was to assess the feasibility and acceptability of the National Institute on Drug Abuse (NIDA) Phenotyping Battery (PhAB), a novel package of self-report and neurobehavioral performance measures assembled by NIDA in consultation with an addiction expert workgroup. The PhAB is designed for eventual use in clinical trials to allow for classification of individuals with SUD along neurofunctional domains (e.g., behavioral phenotype), and to eliminate heavy reliance on DSM-5 criteria and primary drug of use to determine treatment strategies.

For the parent study, participants were recruited from an established patient registry, local advertising, and a SUD treatment clinic. Eligibility criteria were relaxed to recruit a heterogeneous sample of individuals with SUD along with non-substance misusing controls. Thus, individuals in the SUD group were not limited to be in a certain stage of recovery; active substance use was neither an inclusion nor an exclusion criterion. Inclusion criteria for both groups consisted of age between 18 and 70 years and ability to complete forms and interviews in English. Individuals enrolled in the SUD group also had to meet DSM-5 criteria for a current SUD with opioids, cannabis, and/or cocaine as the primary drug diagnosis. Conditions considered exclusionary were: current psychosis, mania, suicidal/homicidal ideation, history of seizures (excluding childhood febrile seizures), or loss of consciousness from traumatic injury for more than 30 min, or any other illness, or condition, which in the opinion of the PI or study physician would preclude safe and/or successful completion of the study. Severe comorbid alcohol use disorder was exclusionary. Subjects meeting severe criteria for more than one drug ($n = 5$) were excluded from this secondary analysis. Non-substance misusing controls met the same criteria noted above, with the exception that they could not meet DSM-5 SUD criteria. All subjects were able to complete forms and interviews in English. At the study visit, subjects completed urine drug testing (UDT), questionnaires, and the PhAB measures.

Measures

The Pittsburgh Sleep Quality Index, PSQI (27), a 19-item self-report tool, assessed overall sleep quality (range 0–21; higher scores indicate worse global sleep) along with seven component scores (range 0–3, higher scores indicate worse sleep). The PSQI is widely used to measure sleep difficulty. It has been validated in a range of settings and in a variety of samples, from children (28) to older adults (29). Based on prior validation studies, a total PSQI score ≥ 5 is associated with poor sleep quality (27).

Demographic information included age, sex (self-reported male vs. female), race, education, and employment status.

Recent substance use was determined via timeline follow-back interview (30) and UDT.

Data Analysis

Analyses were conducted with SPSS version 26 (31) and stratified by sex. First, descriptive statistics were calculated for demographic and clinical characteristics. Continuous variables were summarized via means and standard deviations while categorical variables were summarized via counts and percentages. A series of *t*-tests were conducted comparing sleep characteristics (PSQI total score and component scores) between SUD and control subjects. Next, an additional set of *t*-tests were conducted comparing sleep characteristics between controls and SUD subjects by their primary drug diagnosis (e.g., cocaine, cannabis, and opioid). Lastly, a series of Crosstab analyses were used to investigate whether SUD and control subjects differed in the proportion with PSQI-defined poor sleep (i.e., PSQI ≥ 5).

RESULTS

Data were available for 162 males (44 controls, 118 SUD) and 146 females (64 controls, 82 SUD). Among male SUD subjects, about a third had a primary drug diagnosis for OUD ($n = 53$), followed by cocaine ($n = 37$) and cannabis ($n = 28$) use disorder. For female SUD subjects, OUD ($n = 46$) was the most common primary drug diagnosis followed by cannabis ($n = 22$) and cocaine ($n = 14$) use disorder. More SUD subjects identified as Black race (males 79%, females 73%) compared to controls (males 39%, females 39%; **Table 1**). Among SUD subjects, polysubstance use was common. For example, 45% of male OUD subjects

TABLE 1 | Demographic, clinical, and sleep characteristics of SUD and non-substance misusing control study participants.

	Males ($n = 162$)					Females ($n = 146$)				
	Control ($n = 44$)	**All SUD ($n = 118$)**	**Opioid UD ($n = 53$)**	**Cocaine UD ($n = 37$)**	**Cannabis UD ($n = 28$)**	**Control ($n = 64$)**	**All SUD ($n = 82$)**	**Opioid UD ($n = 46$)**	**Cocaine UD ($n = 14$)**	**Cannabis UD ($n = 22$)**
Demographics	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age	37.0 (15.8)	44.6 (12.4)	44.4 (10.4)	52.2 (9.4)	35.0 (12.7)	34.8 (13.7)	41.2 (13.1)	41.1 (12.5)	50.9 (6.6)	35.3 (14.1)
Race	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Black/African American	17 (38.6)	93 (78.8)	39 (73.6)	37 (100.0)	17 (60.7)	25 (39.1)	60 (73.2)	34 (73.9)	12 (85.7)	14 (63.6)
White/Caucasian	22 (50.0)	20 (16.9)	112 (0.8)	0 (0.0)	9 (32.1)	26 (40.6)	18 (22.0)	11 (23.9)	1 (7.1)	6 (27.3)
All other races	5 (11.3)	4 (3.3)	2 (3.8)	0 (0.0)	2 (7.2)	12 (18.8)	3 (3.6)	1 (2.2)	1 (7.1)	1 (4.5)
Ethnicity										
Hispanic/LatinX	1 (2.3)	3 (2.5)	1 (1.9)	1 (2.7)	1 (3.6)	2 (3.1)	1 (1.2)	1 (2.2)	0 (0.0)	0 (0.0)
Non-hispanic/LatinX	40 (90.9)	108 (91.5)	50 (94.3)	33 (89.2)	25 (89.3)	59 (92.2)	75 (91.5)	43 (93.5)	12 (85.7)	20 (90.9)
Marital status										
Never married	26 (59.1)	58 (49.2)	24 (45.3)	16 (43.2)	18 (64.3)	36 (56.3)	50 (61.0)	28 (60.9)	6 (42.9)	16 (72.7)
Married/living with partner	12 (27.3)	32 (27.1)	17 (32.1)	10 (27.0)	5 (17.8)	21 (32.8)	17 (20.8)	10 (21.8)	3 (21.4)	4 (18.2)
Separated/divorced/Widowed	5 (11.4)	27 (22.9)	11 (20.7)	11 (29.7)	5 (17.9)	7 (10.9)	14 (17.0)	7 (15.2)	5 (35.7)	2 (9.1)
Past 30 days employment										
Full-time (35+hours/week)	16 (36.4)	40 (33.9)	20 (37.7)	7 (18.9)	13 (46.4)	24 (37.5)	18 (22.0)	12 (26.1)	2 (14.3)	4 (18.2)
Part time	8 (18.2)	22 (18.6)	9 (16.9)	6 (16.2)	7 (25.0)	15 (23.4)	8 (9.7)	3 (6.5)	1 (7.1)	4 (18.2)
Unemployed	5 (11.4)	37 (31.4)	19 (35.8)	15 (40.5)	3 (10.7)	3 (4.7)	36 (43.9)	21 (45.7)	8 (57.1)	7 (31.8)
Other	13 (29.5)	18 (15.2)	4 (7.5)	9 (24.3)	5 (17.8)	22 (34.4)	19 (23.2)	9 (19.5)	3 (21.4)	7 (31.7)
Education										
<High school	1 (2.3)	18 (15.3)	10 (18.9)	5 (13.5)	3 (10.7)	1 (1.6)	14 (17.1)	8 (17.4)	5 (35.7)	1 (4.5)
High school or GED	5 (11.4)	53 (44.9)	25 (47.2)	20 (54.1)	8 (28.6)	10 (15.6)	43 (52.4)	25 (54.3)	8 (57.7)	10 (45.5)
Some college	21 (47.7)	34 (28.8)	14 (26.4)	10 (27.0)	10 (35.7)	22 (34.4)	20 (24.4)	11 (23.9)	1 (7.1)	8 (36.4)
College degree or more	17 (38.6)	13 (11.0)	4 (7.5)	2 (5.4)	7 (25.0)	29 (45.3)	5 (6.1)	2 (4.3)	0 (0.0)	3 (13.6)
Sleep	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
PSQI global score (0–21)	5.11 (3.08)	6.92* (3.72)	7.62* (3.80)	5.62 (3.55)	7.36* (3.43)	5.66 (2.53)	7.27* (2.99)	7.63** (2.83)	6.21 (3.26)	7.19* (3.12)
Sleep quality (0–3)	0.86 (0.80)	1.28* (0.95)	1.40* (0.85)	1.14 (1.06)	1.25 (0.97)	1.19 (0.59)	1.41 (0.80)	1.37 (0.83)	1.50 (1.09)	1.43 (0.51)
Sleep latency (0–3)	0.73 (0.73)	1.25** (0.86)	1.37** (0.82)	1.11* (0.88)	1.21* (0.92)	0.91 (0.77)	1.26* (0.74)	1.35* (0.71)	1.21 (0.70)	1.10 (0.83)
Sleep duration (0–3)	0.52 (0.82)	1.24** (1.23)	1.17* (1.22)	1.35* (1.30)	1.21* (1.20)	0.64 (0.86)	1.04* (1.15)	1.13* (1.19)	0.86 (1.17)	0.95 (1.07)
Sleep efficiency (0–3)	1.41 (1.45)	1.15 (1.41)	1.37 (1.46)	0.41* (1.04)	1.75 (1.38)	0.95 (1.40)	1.20 (1.45)	1.35 (1.48)	0.64 (1.28)	1.24 (1.48)
Sleep disturbance (0–3)	0.82 (0.45)	1.12** (0.48)	1.21** (0.50)	1.03* (0.44)	1.07* (0.47)	0.97 (0.40)	1.15* (0.42)	1.17* (0.38)	1.14 (0.53)	1.10 (0.44)
Sleep medication (0–3)	0.14 (0.41)	0.29 (0.64)	0.44* (0.78)	0.11 (0.31)	0.25 (0.65)	0.17 (0.46)	0.56* (0.82)	0.67 (0.87)	0.29 (0.61)	0.48 (0.81)
Daytime dysfunction (0–3)	0.64 (0.65)	0.59 (0.70)	0.65 (0.71)	0.49 (0.69)	0.61 (0.69)	0.83 (0.72)	0.67 (0.74)	0.59 (0.72)	0.57 (0.65)	0.90 (0.83)

*PSQI scores are missing for one male with opioid and one female with cannabis use disorder (UD). The * symbol indicates the differences between groups significant at $p < 0.05$. The ** symbol indicates the differences between groups significant at $p < 0.01$.*

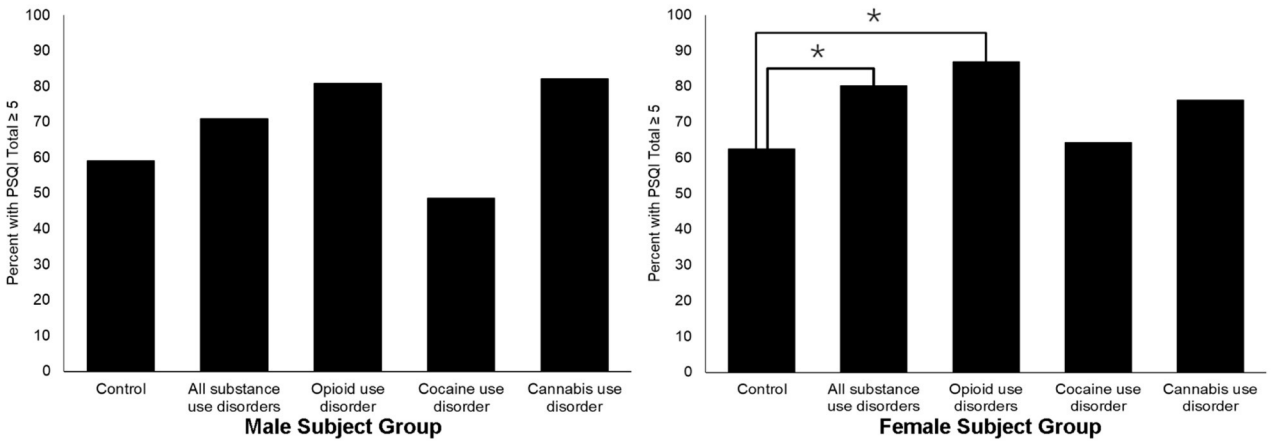

FIGURE 1 | Sex-specific prevalence of PSQI score ≥5 for SUD and control study subjects. The *symbol indicates the differences between groups significant at $p < 0.05$.

reported past 30-day cocaine use with 34% ($n = 18$) having a UDT positive for cocaine. For female OUD subjects, 33% and 26% reported past 30-day cannabis and cocaine use, respectively, with 17% ($n = 8$) testing positive for each of these substances. A third of male and half of female OUD subjects were receiving medication treatment such as buprenorphine or methadone (data not shown).

In males, PSQI global scores were better among controls ($M = 5.11$, $SD = 3.08$) than in SUD subjects ($M = 6.92$, $SD = 3.72$), $t_{(159)} = -2.88$, $p = 0.005$. Male controls also had significantly lower PSQI global scores than males with primary drug diagnoses of OUD ($M = 7.62$, $SD = 3.80$) and cannabis use disorder ($M = 7.36$, $SD = 3.43$), $p = 0.001$, and 0.005, respectively. Generally, male controls reported statistically shorter sleep latency, longer sleep duration, and less sleep disturbances than SUD males with any primary drug diagnosis.

In females, PSQI global scores were better among controls ($M = 5.66$, $SD = 2.53$) than in SUD subjects ($M = 7.27$, $SD = 2.99$), $t_{(143)} = -3.45$, $p = 0.001$. Female controls also had significantly lower PSQI global scores than females with primary drug diagnoses of OUD ($M = 7.63$, $SD = 2.83$) and cannabis use disorder ($M = 7.19$, $SD = 3.12$), $p < 0.001$ and 0.05, respectively. Unlike their male counterparts, female controls did not report any PSQI component score that was statistically better across all primary drug diagnoses for SUD subjects. Refer to **Table 1** for a complete listing of comparisons of PSQI-reported sleep across sexes and study groups.

Lastly, the proportion of males who reported PSQI-defined poor sleep did not differ between controls and SUD subjects, χ^2 (1, $N = 161$) = 2.05, $p > 0.05$, nor primary drug diagnosis SUD subgroups. However, for females, a significantly lower proportion of controls reported PSQI-defined poor sleep than SUD subjects, $\chi^2(1, N = 145) = 5.64$, $p < 0.05$, or subjects with a primary drug diagnosis of OUD, $\chi^2(3, N = 145) = 8.63$, $p < 0.05$. Refer to **Figure 1** for a graphical depiction of group differences in the proportion of individuals with PSQI-defined poor sleep.

DISCUSSION

Sleep is an important component of health that can have widespread medical and psychosocial impacts (32). In our sample of individuals with SUD, we found poor sleep to be more prevalent compared to a control group for both males and females. These sleep differences were most notable for individuals with OUD and cannabis use disorder. However, only for females was overall poor sleep quality more prevalent among individuals with SUD compared to non-substance misusing controls.

In line with our hypotheses, PSQI scores indicated worse sleep quality among individuals with SUD compared to controls. This finding was expected given the emerging understanding of the bidirectional relationship between SUD and sleep (14). However, when we assessed differences from controls by primary drug diagnosis, consistent differences emerged for individuals with opioid and cannabis use disorder. These findings are consistent with literature highlighting the negative physiological effects opioid and cannabis use can have on sleep (18). More work is needed to better elucidate the underlying mechanisms of these associations within other clinical SUD populations.

The interplay between sleep and SUD is likely complex, resembling a co-existing comorbidity where precise functional interactions between sleep, sex, circadian rhythm, and other biological factors are unknown (13). Variation on an individual level could stem from both the specific substances being used and the biopsychosocial context (32), with many factors potentially related to both poor sleep and SUD progression. Our sample recruited from an outpatient clinic and its surrounding community were largely Black, underemployed, unmarried, and with low levels of completed education. This demographic snapshot reflects the high burden of social determinants of health common among many people with SUD, potentially reflecting social indicators of poverty and structural racism, which can also differentially impact sleep by one's gender (33). Importantly, social determinants of health play important roles in sleep health, and there is a call for further investigations into the mechanisms

underlying disparities in sleep disruption using socio-ecological models (32, 33). Taken together, future research focused on sleep's intersection with SUD should incorporate multidimensional frameworks (34), tailored by sex and gender, in their study designs, analyses and interpretations.

When comparing control and SUD groups on clinically significant poor sleep quality (e.g., PSQI score of 5 or more), differences emerged for females only. Sleep disorders are more prevalent among females than males (35). Proposed underlying mechanisms for this disparity are numerous, from the role of sex-specific hormones (36) to social factors that more commonly impact females (33). However, the differential association of sleep and SUD presentation for females compared to males is novel. Our results indicate the importance of incorporating sex-stratified analyses into subsequent work aimed to better characterize the relationship between sleep and SUD.

The main limitation is the small sample size from a single site. This limitation precluded our ability to assess effect modification by sex in multivariable models, an area for future work. Further, age differed by sex and SUD groups, and will need to also be addressed in these investigations. The exclusion of subjects meeting DSM-5 severe criteria for alcohol use disorder may have limited generalizability, but doing so allowed us to focus on sex-specific associations between drug use disorders and sleep, an area lacking in research (37) more so than alcohol (38). Additionally, we did not examine study objectives by gender as gender identity was not assessed in the parent study. Gender influences risks for SUD (7) and poor sleep (33), and gender minority individuals are a high-risk population for SUD (39). Next, recruitment for the parent study was aimed at composing a "real world" SUD sample. This was a strength of the study. However, the SUD group varied widely in stages of recovery, from abstinence to active substance use. The sleep and SUD relationship is complex, stemming from a host of factors, including the direct effects of substance use (16). Future research at this intersection of sleep, SUD and sex should target SUD samples representing specific stages of treatment and recovery, such as individuals receiving medication for opioid use disorder. Lastly, our cross-sectional analyses prohibit conclusions regarding causality between sleep and SUD pathogenesis. Our results are intended to provide a foundation for future studies focused on identifying opportunities for targeting sleep as an avenue to mitigate harms related to SUD in a sex-informed way.

CONCLUSION

Sleep problems and SUD substantially overlap neurobiologically as well as in their socio-ecological complexity. Sleep dysfunction and SUD differ by sex, as sex is one of the critical variables that shape an individual's overall health and daily functioning. Our results begin to shed light on the role of sleep dysfunction in SUD that needs to be addressed in a sex/gender-tailored way. Future work focused on the intersection of SUD and sleep should prioritize investigations of their interplay with sex, gender and social determinants of health to identify options for new SUD treatments specific to an individual as a part of his/her/their biopsychosocial profile.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Virginia Commonwealth University IRB (IRB# HM 20012559). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM, JD, LK-M, FM, and DS conceptualized the manuscript. ED and JD performed data analysis. CM, JD, LK-M, ED, FM, and DS participated in interpretation of the results. CM and JD drafted the initial manuscript. TR, LK-M, ED, FM, and DS provided substantial revisions to the manuscript. FM and DS supervised the project. All authors reviewed and approved the final manuscript and the order of authors.

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Pre-Exposure Prophylaxis Barriers, Facilitators and Unmet Need Among Rural People Who Inject Drugs: A Qualitative Examination of Syringe Service Program Client Perspectives

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Background: People who inject drugs (PWID) are at high risk for HIV infection, yet in rural areas PWID are understudied with respect to prevention strategies. Kentucky is notable for heavy rural HIV burden and increasing rates of new HIV diagnoses attributable to injection drug use. Despite high need and the strong evidence for Pre-Exposure Prophylaxis (PrEP) as a gold-standard biomedical HIV prevention tool, scale up has been limited among PWID in Kentucky and elsewhere. This paper explores individual, environmental, and structural barriers and facilitators of PrEP care from the perspective of PWID in rural Kentucky.

Methods: Data are drawn from an ongoing NIH-funded study designed to adapt and integrate a PrEP initiation intervention for high-risk PWID at point of care in two rural syringe service programs (SSPs) in southeastern Kentucky. As part of this initiative, a qualitative study guided by PRISM (Practical, Robust, Implementation, and Sustainability Model) was undertaken to gather SSP client perspectives on intervention needs related to PrEP, competing needs related to substance use disorder, as well as tangible supports for and barriers to PrEP uptake. Recruitment and interviews were conducted during September-November 2021 with 26 SSP clients, 13 from each of the two SSP sites. A semi-structured guide explored injection behaviors, SSP use, knowledge of PrEP, perceived barriers to PrEP, as well as aspects of the risk environment (e.g., housing instability, community stigma) that may impact PrEP uptake. Interviews were digitally recorded, transcribed verbatim and verified by project staff. A detailed coding scheme was developed and applied by independent coders using NVivo. Coded transcripts were synthesized to identify salient themes in the data using the principles of thematic analysis All study procedures were approved by the University IRB.

Results: Participants were 96% white, 42% female, with a median age of 41 years (range 21–62); all reported injection use within the past month. Overall, we found low

PrEP awareness among this sample, yet interest in PrEP was high, with several indicating PrEP is urgently needed. Clients reported overwhelmingly positive experiences at the SSPs, considering them trusted and safe locations to receive health services, and were enthusiastic about the integration of co-located PrEP services. Lack of basic HIV and PrEP knowledge and health literacy were in evidence, which contributed to common misperceptions about personal risk for HIV. Situational risks related to substance use disorder, particularly in the context of withdrawal symptoms and craving, often lead to heightened HIV injection and sexual risk behaviors. Stigma related to substance use and HIV arose as a concern for PrEP uptake, with several participants reflecting that privacy issues would impact their preferences for education, prescribing and monitoring of PrEP. Noted tangible barriers included inconsistent access to phone service and transportation. Primary supports included high levels of insurance coverage, consistent pharmacy access, and histories with successful medication management for other health conditions.

Conclusions: Drawing on the critical perspectives of people with substance use disorder, our findings provide important and actionable information on individual and environmental barriers and facilitators of PrEP uptake among rural PWID at high risk for HIV infection. These data will drive the adaptation and implementation of a client-centered approach to integrated PrEP care within rurally located SSP settings to address unmet needs for PrEP care.

Keywords: HIV prevention, people who inject drugs, PrEP, stigma, rural, implementation science

INTRODUCTION

Despite decades of notable scientific advances in HIV prevention and treatment among highly affected populations (1) people who inject drugs (PWID) remain at high risk for HIV infection. A recent global review demonstrated that PWID continue to be severely impacted by HIV, with 9.0% of PWID in North America estimated to be living with HIV (2). Since 2015, HIV outbreaks among PWID in the US have occurred with increasing frequency in lower population rural communities (3–6), and Kentucky is notable for heavy rural HIV burden and increasing rates of new HIV diagnoses attributable to injection drug use (7). Nevertheless, rural PWID are generally understudied (8) and as such, critical information on uptake of HIV prevention services, including Pre-Exposure Prophylaxis (PrEP) is largely unavailable. Although numerous behavioral and structural interventions have successfully targeted PWID (9–14), virtually all have been in urban areas, and until recently most have not involved PrEP.

The World Health Organization added PrEP to the recommended combination HIV prevention package for PWID in 2014 (15) and in 2015 issued guidance for PrEP implementation in PWID (16). To date, the strong scientific evidence-base for PrEP as a gold-standard biomedical HIV prevention tool has not translated to optimal clinical care, with scale up in the US modest overall (17), and particularly among PWID (18). Kentucky is no exception, with an estimated 11.4% of individuals with an indication for PrEP receiving PrEP coverage in 2020, one of the lowest rates in the nation (19). Barriers to PrEP implementation among PWID are multi-level. At the individual level, awareness of PrEP and perceived risk for HIV is modest in recent studies with PWID (20, 21). Noted structural barriers include the cost of obtaining PrEP medications, housing instability, and lack of secure medication storage options (21–23). In rural areas specifically, structural barriers include long distances to PrEP providers, limited availability of health care providers and testing sites in general, and high levels of stigma surrounding HIV factors (24–29). Clinical barriers in rural healthcare sites also reflect poor infrastructure and capacity for PrEP delivery, lack of PrEP knowledge among staff, and absence of local PrEP providers (30) leading to PrEP "deserts" (31, 32). Although supports for PrEP uptake among PWID are less widely described, Allen et al. (21) recently found that integration of PrEP services into venues that PWID routinely access would help to optimize PrEP awareness in communities where there is low background knowledge of PrEP.

This paper explores individual, environmental, and structural barriers and facilitators of PrEP care from the perspective of PWID in rural Kentucky. Using qualitative approaches guided by the PRISM (Practical, Robust, Implementation, and Sustainability Model) implementation science framework (33), we elicited PWID's perspectives on their risk environment (34–36), as well as sources of support and preferences for PrEP care access that may influence PrEP uptake. Rural Appalachian PWID are situated in environments characterized by high levels of stigma related to substance use (37), unstable housing, fear of arrest, economic distress, and inadequate access to services (38–41), which underscores the need for interventions

that address multi-level barriers to improve HIV prevention outcomes. Nevertheless, rural PWID also demonstrate notable resilience and motivation for health improvement, including uptake and consistent use of SSPs to obtain sterile injection equipment (40). This manuscript examines rural PWID's lived experiences to systematically assess PrEP barriers, facilitators and unmet needs, which will inform and guide adaptation of a PrEP-focused intervention to expand access in rural care settings.

METHODS

Data are drawn from an ongoing NIH-funded implementation study designed to adapt and integrate a PrEP initiation intervention for high-risk PWID at point of care in two rural Appalachian syringe service programs (SSPs) in southeastern Kentucky. We used the PRISM (Practical, Robust, Implementation, and Sustainability Model) framework (33) to guide this project. PRISM assesses organizational and individual level contextual factors that may contribute to implementation outcomes, specifically examining elements of the external environment, program or intervention design, implementation and sustainability infrastructure, and the multi-level recipients of an intervention (organizations, providers, and clients) to understand barriers and facilitators to implementation.

Study Sample

Participants were recruited through in-person contacts by the study team who were present on site during operating hours of the participating SSPs. These programs are integrated into regular health department operations in Knox and Clay Counties in rural southeastern Kentucky; the SSPs have been operational since 2016 and 2017, respectively. In addition, the Clay County Health Department operates a mobile SSP 1 day per week in a remote location to provide sterile syringe access in outlying areas. Both Knox and Clay Counties are entirely non-metropolitan based on Rural-Urban Continuum Code indicators. Eligible participants were age 18 or over and reported use of the SSP and injection drug use at least once in the past 30 days. Twenty-six PWID participants enrolled and completed qualitative interviews between September and November 2021.

Study Procedures

Study enrollment and in-depth interviews were conducted in two county health department fixed site SSPs, as well as one mobile site. Brief study eligibility screening was conducted by a study team member, which included collecting age and other basic demographic information, as well as questions on recent substance use patterns and SSP utilization. Study staff reviewed informed consent materials and discussed the provisions of the consent document prior to beginning the interview. Participants were asked to provide written consent that they agreed to participate in the interview and agreed to audio recording.

An experienced qualitative researcher facilitated the one-on-one interviews in a private room within the fixed SSP locations, and at a private outdoor space adjacent to the mobile site. These semi-structured, in-depth interviews were organized by an interview guide, focused on the PRISM domains of *clients as recipients of the intervention and client perspectives on the intervention.* Key topical areas included: injection behaviors, HIV risk, SSP use, knowledge of PrEP, perceived barriers to PrEP, physical and mental health care access, use of HIV prevention services, social supports, strengths and resilience, as well as aspects of the risk environment (e.g., housing instability, community stigma) as they impact PrEP uptake. Questions related to PrEP awareness and interest were asked in the final segment of the interview, and were introduced with the following item utilized in prior research (42): *Have you ever heard of HIV-negative people taking a pill every day to reduce their chances of getting HIV infection (this is called PrEP, for Pre-Exposure Prophylaxis)*? For clarity, participants were simultaneously shown the *PrEP 101* consumer fact sheet developed by the Centers for Disease Control and Prevention. Interviews lasted between 30 and 60 min. A $30 gift card incentive was provided to participants upon interview completion. Institutional Review Board approval for the study was obtained from the University of Kentucky Medical IRB.

In-depth Interview Data Analysis

Four primary steps were taken to analyze the textual data elicited in the in-depth interviews. These included: (1) initial verbatim transcription and verification of interview audio recordings; (2) focused readings of these transcripts; (3) the construction and application of a detailed coding scheme; and (4) the compilation of core explanatory categories from the analysis of the transcripts and the construction of an interpretive summary based on the interview codes. Interviews were recorded and transcribed verbatim using a HIPAA-compliant transcription service. Interview transcripts were then reviewed and verified for accuracy by a member of the research team. Guided by PRISM domains, and an initial reading of the transcripts, the research team developed a coding scheme for the interview data in NVivo (43), using a hybrid deductive-inductive approach (44). Initial codes were primarily deductive, sourced largely from the relevant domains of the PRISM framework and initial readings of a small subset of transcripts. Subsequently, inductive approaches that drew on salient information in the raw data were utilized to further develop the codebook and account for new or unanticipated patterns of responses. Several members of the study team are experienced qualitative researchers and served as independent coders; at least two members of the research team coded each interview transcript. The research team met weekly to discuss coding progress and achieve consensus on coding consistency, and to evaluate whether new codes were identified that indicated novel emerging themes, and whether existing codes needed further refinement. The coded transcripts were merged and synthesized to identify the primary themes in the data using the principles of thematic analysis (45).

RESULTS

Table 1 displays basic demographic, health, and social characteristics of the interview participants. Overall, participants were 96% white, 42% female, with a median age of 41 years (range

TABLE 1 | Syringe service program participant characteristics and pre-exposure prophylaxis perceptions ($N = 26$).

	***N* (%)**
Demographics	
Gender	
Female	11 (42.3%)
Male	15 (57.7%)
Race/ethnicity	
Black/African American	1 (3.8%)
White, non-hispanic	25 (96.2%)
Age (*Median; Range)*	41 (21–62)
Current drug injection*	
Methamphetamine	9 (34.6%)
Buprenorphine	15 (57.7%)
Heroin	3 (11.5%)
Prescription opioids	1 (3.8%)
Health and social factors	
Current health insurance	26 (100%)
Arrest/incarceration history	14 (53.8%)
Hepatitis C positive	15 (57.7%)
Healthcare services utilization	
Lifetime substance use treatment	19 (73.1%)
Currently prescribed buprenorphine	8 (30.8%)
Lifetime HIV testing	21 (80.8%)
PrEP perceptions	
PrEP awareness	7 (26.9%)
PrEP interest	19 (73.1%)

**Adds to >100%, responses not mutually exclusive.*

21–62). All reported injection use and SSP use within the month prior to interview, including one participant using the SSP for the first time on the day of interview. Twenty-one participants (80.8%) reported using the SSP for at least 1 year, and 19 (73.1%) reported visiting the SSP at least monthly. Nearly three quarters of participants reported histories of formal substance use treatment, involving either residential or outpatient care, or medication treatment involving buprenorphine. Additionally, more than half described experiences involving arrest, detention, and incarceration, indicating significant histories of contact with the justice system among the individuals interviewed. Notably, nearly 60% reported Hepatitis C (HCV) positive status tied to risky injection practices. Approximately 80% of participants had ever been tested for HIV, and the majority (61.5%) had done so within the past 6 months at the SSP. Overall, there was low baseline PrEP awareness among this sample (26.9%), yet interest in PrEP was high, with 73% indicating a desire to learn more about PrEP for personal use.

Barriers and Supports for PrEP

Our systematic examination of barriers and facilitators of PrEP care revealed several key themes related to uptake of this HIV prevention tool. **Table 2** displays a summary of the primary themes that emerged in analysis mapped to the relevant PRISM domains that were activated.

Barriers: Knowledge and Beliefs

Overall, a lack of basic HIV and PrEP knowledge was in evidence among interview participants. Participants were uniform in stating that they did not have exposure to HIV prevention education or messages in their communities of residence and did not hear HIV discussed as a priority health issue. In fact, even among those reporting awareness of PrEP, their exposure was often incidental through media, advertisements, or other sources outside of their home communities. An emergent theme in participants' narratives centered on an *unmet need for HIV-related information, and related uncertainty in gauging personal risk and managing prevention.* In this regard, participants largely relied on informal or sporadic sources for HIV prevention information that framed their views and concerns around risk. This uncertainty was consistently noted as a source for complacency and ambivalence by several participants:

> *I don't know, you don't really hear much about it. You just hear people talk about people. But you know, you don't hear much about it. You really don't. A lot of people don't think about it. (Male, 50s)*

> *There ain't no AIDS around here. If there is and they're made aware of that. That would make this that much more important to them. Uh, most people, when you hear AIDS you think of homosexuality, you think of cities, you don't think that the good old boy out in Gertler, Barbourville has it. You know what I mean? Uh, I think maybe if they knew how prevalent it was, or even if it, I don't know if it's prevalent around here even. And I pride myself on being informed. (Male, 40s)*

This context of uncertainty fueled by limited information pervaded personal risk evaluations as well. Many participants expressed fear of HIV due to the lack of a cure, uncertainty about testing and treatments, and relied on informal awareness of HIV-positive individuals in their small communities to understand prevalence:

> *I used to, and I get scared thinking if I got it, I don't know if I want to find out. But now you're more likely to die with it, than from it. You know what I mean? A lot of people still see it a death sentence, I guess. (Female, 40s)*

> *But I actually probably need to do it again. It's been a long time. I don't feel, I feel all right. For some reason, I can't gain no weight. I eat a lot. And I'm not gaining weight. I don't know why. I don't think… I think I don't have it, but I shouldn't think like that. I need to get tested, now that you say that. I mean, I want to. Just to see, to make sure I don't have anything. (Male, 50s)*

> *I get nervous every time, no matter what, getting tested for stuff like that. That's the most terrifying thing. Like back in the day I watched people die from Hep-C. So when I got it, I flipped out and now they have a cure. I mean, but HIV they're really behind. Not behind, they're catching up really well with the treatment. Now there's treatments they can live with it, right? (Female, 30s)*

> *Yeah, I've got a couple friends with it. Yeah, I got a girl, and her man, and another one, and another one, and another one. Yeah. I know five or six got it. I walked up to their house and I was going to smoke a joint with them. And they said, "Hey, probably best you*

TABLE 2 | Primary Themes for HIV Prevention and PrEP Uptake among Rural PWID Mapped to PRISM Domains.

PRISM domain	PRISM element activated	Theme	Example quote
Recipients, client characteristics	Knowledge and beliefs	Need for HIV information	*There ain't no AIDS around here. If there is and they're made aware of that.*
		Uncertain personal risk	*I get scared thinking if I got it, I don't know if I want to find out.*
	Disease burden	Substance use disorder situational risks	*When you are sick and withdrawing there's no line you won't cross.*
Program (intervention), client perspectives	Addresses client barriers	Stigma: social rejection and harms from systems	*The stigma would be like that. You wouldn't want somebody to know you're taking it [PrEP] because they think you have HIV.*
		Scarce physical capital: pervasive economic distress	*Sometimes I might miss a week cause I ain't got, my ride got tore up and you know, you might not find a ride up here.*
	Access	SSP utilization: safety, inclusion supports expanded care opportunities	*I felt like that I was being taken care of, that someone cared enough that I didn't have to shoot with used needles.*
	Client-centered	Health management: resilience, empowerment, readiness	*I had it [HCV]. And then I took the Mavyret and got rid of it. I took three pills a day for two months.*

just give me a joint." I said, "Why?" They said, "Because I got Hep-C and HIV." I said, "Well, how'd you catch it?" They said both sharing needles with each other. (Male, 30s)

With some exceptions, participants were largely cognizant of both sexual and injection-related risks for HIV but most perceived their personal risk as modest, and markedly lower than in the past. This shift was largely attributed to uptake of the syringe service programs, noted as structural facilitators of reduced injection related risks and sharing behaviors:

I lived in a trap house and there was a hole in the wall and that's where we put our rigs and you just reached in and got one. Uh, and at the time, you know, I was wanting to die anyway, and I really didn't care. So if there had been an exchange over there, I know it would've made a difference. I know it would have made a difference. Maybe not necessarily to me specifically, but at least one person. It would have saved one person from having Hep or HIV. (Female, 30s)

Nevertheless, several participants were candid about episodes of ongoing injection risk that remain, identifying aspects of *substance use disorder severity as critical to unanticipated situational risks*. Situational risks were most apparent in the context of withdrawal symptoms and craving, which were often tied to heightened injection risk behaviors:

I remember me not being able to get my shot and I was sick for like four days. And subutex, suboxone withdrawals, that's a whole other story, it hurts, it hurts your bones. Um, but I remember I didn't get up off the couch. I was trying to go [inject] in my hands, and I didn't get up to do, to rinse it out or nothing. I just kept on trying and trying and trying. (Female, 30s)

When you are sick and withdrawing there's no line you won't cross. (Male, 40s)

Yeah, it's such an overwhelming urge when you're sick, you feel it, uh, I could explain it a hundred different ways and, and I hope to God, you never have to experience it with yourself or any of your loved ones. There's no stronger of a driving force than a detox, than a withdrawal. (Male, 40s)

Barriers: Stigma and Rejection

The background experience of interview participants as PWID, members of a highly stigmatized group within small rural communities, was apparent in many aspects of their narratives. A key theme in this regard related to *social rejection from both individuals and systems, and lived experience of harms from systems*, be they justice systems, treatment systems, or healthcare systems. Interview narratives reflected a deeply felt absence of community membership, or social capital, with several participants describing their location in marginal spaces on the boundaries of the community. Individual accounts of justice issues are illustrative of systems harms that shape individuals' experiences of safety and surveillance:

We can't get no help from the police. Because they hate on us because around here, if you don't come to 'em with your hat in your hand. (Male, 50s)

I'm harassed on a daily basis here. I mean, when I pull out of a gas station down in town, they all just turn their lights on. I about wrecked the other day, and they pulled my britches down in public trying, looking for drugs at a mother fucking gas station. I'm allowed. I mean, that's not legal. And they're a bunch of kids, that's what it is. But somebody's telling them what to do. And because they don't even know me. (Male, 50s)

They used to harass me a lot but they don't no more. Me, my family before that. It's just, I don't know. They just didn't like our last name or something. I don't know. Which, you know, I did get pissed at 'em because they lied on me and they tried to send me to prison and stuff for stuff I didn't do, and it really made me angry. I hate 'em for it. Like, uh, if somebody shot me up there, we wouldn't call the cops. I just don't like 'em and they don't like me. The reason I don't like 'em is because you always got the pricks you got to deal with. They want to judge you and they want to accuse you of stuff you ain't done. And so I don't fool with them and they don't say anything to me no more. I have no trust with them whatsoever. They'll figure out something to charge you with. I guess it felt like that all my life. The issues is if you're not kin to them or a snitch, they don't like you. (Male, 40s)

They arrested me on that possession and the paraphernalia charge. They still go stack 29s [warrant checks] on me at least three times a week. To see if I got warrants on, and I've been out of jail two years or longer. And they still three, four times a week. Still to these days they'll run my name, every time they see me. They stop me. (Male, 40s)

These pervasive stigmatizing interactions have important implications for understanding uptake of treatment and healthcare among PWID, including PrEP. Adverse experiences in treatment settings were commonly reported, with interview narratives describing these episodes as inappropriate, unhelpful, or even directly harmful, creating feelings of mistrust, humiliation, and injury. Interview participants noted deficits in accessing care that was evidence-based, that allowed medication, or that followed best practices for retention in care, which frequently resulted in internalized stigma:

I felt deceived at the place that I went to. I graduated. I did everything that's asked of. And they asked me, said, what was you going to do when you graduate? I said, I'm going back home to my wife. And they said, well, we don't think that's a good idea. I said, well, you asked me what I was going to do. Well then, we think you should take the second program here. I said, I want to talk to my PO and I said, Hey, do I have to? Because prison is the one that sent me. And he said, no, you just have to go through phase one. I said, do they know that? He said, yeah, they know that, but they try to make you think. And he was just honest with me. (Male, 40s)

Yeah, they have 100 people. If somebody messes up, they don't get to go outside and smoke or nothing. So, you have to get up at five o'clock in the morning and make your bed, and I never did like orders, so I didn't get along with it. They get up and you got to tell them what choice of drugs you got to do, in front of 100 people. And I was the type that, hey, I'm a drug head. I mean, it's simple. I mean, I don't want to talk. And I didn't want to look stupid in front of 100 people, because here I am in rehab for the same reason. Drugs. And yeah, I got in there and I stayed, like, 15 days out 90, and got kicked out. They kicked me out. They said I had suboxone in my system. And they wouldn't give me my Seroquel, so I had to come back to Clay County, like 200 miles away and get my Seroquel. They didn't know the pharmacy number, they didn't know what they was doing. So, yeah, pretty much they was trying to make a joke out of me. I'm afraid to go back to a suboxone clinic, where I'm court ordered, they'd probably put me in jail. So, I'm scared. (Male, 30s)

The courts kind of screwed me. They said all I had to do was complete a month and then they'd take my felony off. Well, I completed the month, easy, and the people said, "Well, you're doing so well. Uh, how would you like it if you stayed for the 90-day program?" So, I voluntarily stayed for 90 days, but they ended up switching my stuff without telling me, "Well you was only court ordered for 30, but since you want to do 90, we're going to court order it for 90". And then I ended up taking off and I kept my felony and lost my marine corps chance. (Male, 20s)

In a similar way, many participants experienced rejection or exclusion in a variety of healthcare settings that led to subsequent avoidance of care, unwillingness to seek help for acute and chronic health problems, and inability to effectively engage in or uptake disease prevention activities.

Yeah, people, I know people who had abscesses on their arms. They don't go to the hospital cause they talk about 'em. (Female, 30s)

If you ever have to go to the hospital here for something serious, and you go there for something. And they say, well, you got this in your system. Well, yeah, if you would've asked me that, I would've told you. You didn't have to try to trick me into do anything, but I'm here because of this, not because of that. And then they look at you totally different.…Can you fix what's wrong with me? That's all I want. So I said, first of all, before I even pee in cup, I smoke pot. I do get high, but I still need help for this. Can you guys help me? (Male, 40s)

I met a doctor two, three days ago that very badly upset me. It was a gynecologist and she said, "When was the last time you shot meth?" I said, "Excuse me?" She said, "When was the last time you shot up meth?" I said, "I don't do meth." I mean, that was very upsetting and I didn't think she was even allowed to ask me something like that. This is the first time I've ever met her. So actually I don't want to meet her again. She made me feel like I was about "… that big." (hand gesture indicating small size). (Female, 50s)

At the emergency room they will barely even give me an ibuprofen because where I inject drugs and stuff like that. And one time I sprained my ankle, well that's why I'm walking around with a sprained ankle right now because, uh, they ain't no sense in going over there cause they ain't gonna do nothing for me. Because where I've been injecting drugs, they got it wrote down in the paperwork that I'm an IV drug user. So they won't give me nothing for pain and nothing to help me out. So I have to get mine off the street. (Male, 30s)

You go to a pharmacy here and you ask to purchase them [syringes]. Right. They're going to shut you down real quick. They don't want to help you. (Female, 30s)

Background experiences of stigma and social exclusion had a strong connection to HIV prevention attitudes among interview participants. For some, HIV was feared as another potential source of social rejection, while for others, HIV prevention methods were also seen as potentially stigmatizing, by indirectly disclosing involvement in injection or sexual risk behaviors.

Stigma related to HIV arose as a direct concern for PrEP uptake, with several participants reflecting that privacy issues would impact their preferences for education, prescribing and monitoring of PrEP. For some, stigmatizing experiences with HCV diagnosis were called to mind, driving the prioritization of privacy around PrEP care for HIV:

They shun people with it. You know, I don't judge no one. Who am I to judge? I mean, I may not like what you're doing, but I don't dislike you for it. (Male, 50s)

Oh, if someone has it, they'd probably talk about them like a dog. It'd make it, it'd be a hard time on 'em, they'd probably have to move away. To be honest with you, they look at you different, down on you, you know. (Male, 50s)

It would be terrible because I was just about the first person in our little holler that tested positive for Hep and I got treated awful. I mean, people, family ignored me, old friends ignored me because they were scared to death. I mean, they didn't know what it was so, which I was scared to death too. (Female, 50s)

I'm sure they wouldn't share it. You know what I mean? That's a very private, like, even me having Hep-C, I would never ever tell anybody, like, I'm very ashamed of it. I'm very embarrassed. So I'm sure it's the same with HIV. You wouldn't want to be around 'em. I mean, when like you're sharing needles and like, "are you sure you don't have HIV"? I got Hep-C, that's cool. I mean, that's how crazy it is. (Female, 30s)

The stigma would be like that. You wouldn't want somebody to know you're taking it [PrEP] because they think you have HIV. (Female, 30s)

If it's something to do with you having it [HIV], you know, then you might want to keep quiet. But no, this is telling them, you know, you're trying to just prevent it, I mean. I don't see nothing bad there. (Male, 50s)

I don't know. I'd be kind of embarrassed just to go get it [PrEP]…people just love to talk in general. (Female, 50s)

Barriers: Scarce Physical Capital

Participants commonly mentioned experiencing strained and scarce personal financial resources, tied to the broader community landscape of declining economic prospects. Even among participants who were not personally impacted by severe economic hardship, interview narratives reflected a palpable theme of *pervasive economic distress and poverty as drivers of risk* for individuals in these rural communities:

I don't know why this area, so there's nothing here. I get that. There's no, there's no, uh, way to prosper, or like have, any kind of future here at all. And I get that, but why has it been so long that it's been going on? This is not a bad place to live. As far as the area is now. It's very pretty here, but there's just not enough. I feel like there's something that holds this area back and I just don't, I'm not sure exactly what it is. Now it's the drugs and you know, people in the, where, where did it all come from? That had to start somewhere because it didn't just happen overnight. It happened over a long period of time. Why didn't we move along like everybody else in the country? (Female, 30s)

I think all these people around here that if you ain't rich, then you can't survive. It's rough.

Like you get pretty much, most people that ain't got money or jobs or stuff like that, they end up homeless, on the streets, and then they end up in jail because they got homeless on the streets doing drugs. (Male, 30s)

While housing opportunities were most often available due to the presence of supportive family members and extended family networks, many participants reported scarce financial resources, income, and employment opportunities that inhibited consistent access to cell phones and personal transportation, which are especially critical in areas that are largely devoid of public transportation systems. These factors were reported as the most common tangible barriers to communication and attendance at health-related visits:

Yeah. I'm kind of working on getting a phone. That's been my biggest thing about the doctor and everything. Because I'm having to…I mean some family members in the house could do, but it's hard to get to use their phone. (Male, 40s)

She was going to call me, and my boyfriend got my phone. I have the worst trouble with him with my phone because he will not leave my phone alone. He thinks he has to have it and use it. It's like we go through a phone a month, me and him do sometimes. (Female, 50s)

I'm still trying to. I might have one today maybe. I actually, I can get a phone up at Walmart for, I think $30 is the lowest one you get up there. I think about going straight up there and just getting a phone. So that would take a lot of stress off of me because at the doctor would have a number that they call. (Male, 40s)

Sometimes I might miss a week cause I ain't got, my ride got tore up and you know, you might not find a ride up here. (Male, 30s)

Just no transportation. I mean, getting there. (Female, 40s)

Although not highly prevalent in this sample, for individuals reporting unstable housing it represented a highly salient barrier to healthcare and PrEP services uptake, deeply impacting all aspects of personal ability to connect with services, to follow a medication regimen and safely store medicines:

Well, I'm homeless. I'm homeless, I'm living in a tent. I have to wonder from day to day where I'm going to be able to lay down, how I'm gonna feed myself, uh, this or that. And how I'm gonna feed my drug at that. Uh, uh, and it's just, a million things going on in my mind everyday. And then I move my tent, like every other day, probably. Cause if you don't, somebody will take it and it's sad to

say, but people will take the place you are now. So you have nothing when you come back. (Female, 30s)

Supports: Syringe Service Program Utilization

As noted earlier, interview participants were recruited from the local syringe service programs in their counties and were current participants in the SSPs. Participants were both novice and experienced SSP utilizers, but most had used the programs for at least 1 year. Participants reported overwhelmingly positive experiences at the SSPs, considering them trusted and safe locations to receive health services. It was quite common to report initial hesitation about the programs due to privacy concerns and concerns around law enforcement activity, but these diminished over time:

I was kind of worried about the cops. That's what scared me. That's what really made me nervous was going to jail. (Female, 50s)

I believe that the policeman used to sit up across the mountain over there and watch and see who came here, when it first started doing it. And I don't think that's right. (Male, 50s)

I wasn't too sure. I don't know, I really never thought much about it. I kind of thought the law or something watched or stuff like that. Because the stuff we do ain't legal, but I was a little concerned always watched for the law and stuff. (Male, 50s)

Well, they were in the back place a lot of times you'd see an unmarked car or a cop used to sit back there. There is one that worked there or something. We didn't know and then you've got people that talk stuff like "they follow you home". And then, you know, sometimes you start wondering because you don't do that stuff that you should do, like selling, stuff like that. So, then you leave here and you don't know what's going on. (Male, 50s)

The biggest difficulties coming to exchange was the fear of people finding out. (Male, 50s)

Key in the trust building process were assurances from peers and program staff about the confidential nature of the programs. Several participants reported being initially referred to the programs by friends and now trying to encourage others to utilize the programs or exchanging for others who are still reluctant to attend. They valued the confidentiality protections of the programs, and privacy was once again highly valued in these small communities. Several clients mentioned being fearful of disclosures if using the program, but none had experienced this.

When people don't understand anything, they pretty much talk negative about it. It goes along with everything, and I've heard a lot of people say I wouldn't go down there for nothing. And I said, well, if you got old ones, give them to me, I'll go up there and I'll exchange it for you. And when I come up here, I tell the ladies that give them to me, what I do with them. I say, when I go up there, I don't use it that many a day, but I help other people out. (Male, 40s)

The lady that was here kind of was like… She didn't come right out and say, "Well, no, we're not going to call the cops or anything like that and tell on you for changing needles, but you do need to have clean needles. That's where we're trying to help you, with trying to get you clean needles and keep clean needles, keep you in the program as long as you do drugs to where you will have clean needles. You won't be injecting with dirty needles and stuff." (Male, 40s)

Well, they don't take your name. Well, they just use the first two letters of your first name and last name. (Male, 30s)

My friend. He come up here and showed me the ropes around here. He introduced me. He's family, well, he ain't family, but he's like family. (Male, 30s)

I started coming at the beginning, let's see here, about two years ago. I found out about it because I was buying needles off people. And then I just got to where I was like, well, if I don't go over to the exchange, and I keep doing what, I'm going to be right back in the hospital for the same crap, you know what I'm saying? I don't want to go through that again. They're always nice to me. And I was worried because I know some of the people, I live around some of the people. I was afraid they might say something to my mom, you know what I'm saying? But they haven't, thank God. Because she would kill me. (Female, 30s)

Participants noted many important benefits of using the SSPs, not surprisingly, enhanced access to sterile needles was consistently reported as the primary benefit of these programs. In these small communities, SSPs were often noted as the only source for obtaining sterile injection equipment:

You was having to buy these needles and stuff and go to people, they're going to charge you a dollar a piece for them. Some people charge $2 a piece for them. You have to end up paying for them every time you get them, and sometimes they won't have them and stuff. I'm afraid they'll give me a dirty needle and say it's clean or something. It kind of worried me if I ever had to. (Female, 50s)

Well, to be honest with you just trying to get needles because it's hard. You can't just go to Walmart here or any place to get them. So you start buying them off people around here and Lord, you pay five, six dollars a needle. So, I did start reusing needles. And so, uh, just from here, they helped out with everything. They really helped out with everybody. (Male, 50s)

I did [shared] when I first started. It's been years ago now. Now I just use a brand new one, one time and when I'm done, I store it and take it to the exchange. And there weren't no blood or anything in it. But I would put bleach in it, clean it out in water and then take a lighter, heat the end of it, that like, it takes all the skin cells and stuff off of it and then do it… we just couldn't get new ones [needles]. (Male, 20s)

I didn't actually share needles. I shared a can that we made enough for three shots, and we all pulled up out of it. You know what I mean? I really don't think I've shared. I've never shared a needle with anyone, but I've used my own needles. Because back in the 2000s, you couldn't get needles like you get them today. And that's why my arm is scarred up a lot too, because they're so dull. And I mean, I've used dull needles. So now, I mean, I'm not proud of it, but it is what it is. (Male, 50s)

In a general way participants described the SSPs as overcoming a long-standing structural risk related to lack of access, and for some this assurance represented an opportunity to be intentional about other health changes, including testing and treatment. Many participants mentioned that using the SSP had allowed them to reduce sharing and re-use behaviors, which they credited with prevention of HCV and HIV, but also acute illnesses and infections:

I've not caught any new diseases and I'm not having to reuse and reuse and cause all them sores on me from, you know, reusing. (Male, 30s)

It [HIV] was on my mind a lot and, uh, um, I guess, um, me being crazy or whatever. Um, never thought about, you know, going to the doctor or something and just went in and start asking for an HIV test. But that's been a real help, like to put my mind at ease. So it's a little off my mind since then, since they started to do it [testing]. (Female, 30s)

I wouldn't have otherwise known, like I know I could go to the doctor or whatever, you can go to the hospital and walk in and say I want to be tested, but other than that, generally I wouldn't off the top of my head think of where to go. So that's a good thing that they have. I wouldn't, I wouldn't have had it done. I wouldn't have had it done any time otherwise. (Female, 30s)

When I started the program [SSP] I thought, well, you know, I'll always have new needles. So I went and got Mavyret [HCV treatment]. (Male, 30s)

Interview narratives related to SSP use crystallized an underlying theme regarding *enhanced safety, inclusion, and community that supported continued SSP use, but also integration of PrEP care*. Participants conveyed a sense of safety, belonging and dignity that pervaded interactions at the SSP and supported meaningful engagement in care. Issuing of SSP cards by the health department was also seen as providing protection from law enforcement, empowering participants to safely and legitimately possess injection equipment:

I like all the people here, they're my friends outside, so I know everybody. (Male, 50s)

I felt like that I was being taken care of, that someone cared enough that I didn't have to shoot with used needles, bad needles. (Female, 50s)

Everyone over there is fantastic because they're all very personable. They're, uh, very knowledgeable. They work with you, you know, they're not like dismissive, you know, they're just a terrific bunch and things, what I've seen. (Male, 50s)

He worked here for a long time. He was good person 'cause he been through the same thing and got saved. And he knew what we're going through. I mean, you know, they don't look down on you. So I always liked him. That's what got me coming here. I was comfortable with him and all of the ladies working here were good. And you know, some places people look at you like a piece of trash or something. Look at you like you're different, but they're always good to me. (Male, 50s)

I've been stopped and had syringes, needles on me. As long as you tell them that you got the needles and where they're at, they'll put them in a container and not charge you with them or whatever. They give us a card, but I can never keep up with it either. They give us a little break. (*Female, 40s*)

These positive care experiences at the SSP set the stage for receptivity to integrated PrEP care among participants. As noted earlier, interest in PrEP was high, with 73% indicating a desire to learn more about PrEP for personal use:

Hell yeah. I mean, if that'd keep me from catching anything, yeah. Hell yeah. Because I had my shots whenever I was little. I might take you up on that pill. For real. (Male, 30s)

I would [be interested]. I would get some people together and try to bring them up here. I know at least two people would come with me. There'd be three. (Male, 40s)

I'd like to take it. How could you get it? I would rather do it without going to my doctor, to be honest with you… it would be great if you could do it here. I am very interested in it, and I know a bunch of people that would be interested in it. If they could do that with the program, the needle exchange, and just offer it. (Female, 30s)

Supports: Successful Health Management

Participants reported a high prevalence of health complications, including HCV infection, overdose, abscess, sepsis, endocarditis, and chronic diabetes, lung, and liver problems, indicating significant life challenges related to co-morbidities. Although these health conditions clearly represent serious stressors, we noted an emergent theme in the interview narratives regarding these background experiences of illness, which particularly with other bloodborne infections, raised awareness of vulnerability and highlighted the value of prevention. Participants expressed *resilience and feelings of empowerment in successfully managing existing health conditions*. Several described taking regular medications for health issues, which supported their readiness and agency to manage PrEP:

I had it [HCV]. And then I took the Mavyret and got rid of it. Three months. I took three pills a day for two months. They said it might give you a headache or something, but I didn't have no side effects. You, but you had to take it every day. If you missed a day, it won't work, well they said it wouldn't but it did. It's wild, it did. (Male, 30s)

I have chronic Hepatitis C. I did have, and I took the medicine to clear that up again. I think I've contracted it back, maybe. Uh, I was tested for HIV just today, but then it was negative. And then, uh, the last time I was tested for Hepatitis C it was over here at the hospital. It was about a year ago. I cleaned it out, cleared it out, took the medicine. (Male, 30s)

With high blood pressure, cholesterol and things like that in general, you know, that is an ongoing thing. As far as conditions, you know, you'd have to have medication sometimes for the rest of your life.

So yeah, it is, you know, a continuous process and everything. I'm diligent about things like that. You know, the doctor says take it, you know, because that way I don't go off on a different path. (Male, 50s)

I have high blood pressure. I get, that's why I get high blood pressure medicine. I take it every evening. I've been getting it for about 3 years now. (Male, 30s)

I had got an infection in my heart, stayed in UK [University of Kentucky] for seven months. It shut my kidneys down. I'd done a bad shot. I had to learn to re-walk. But I got kicked out because my husband come up there, out of his mind, and I didn't get to do my last treatment. So when I come home, I still was septic. Then I got out and had to go back to Pikeville and do heart surgery. And it's the whole backside of my heart, or valve or something. My heart rate's fast. In fact, my whole life. And when they done the heart surgery, it makes my heart overwork. So I take two or three different blood pressure pills, but I ain't got a blood pressure problem. My mother makes sure. I got three girls too. Trust me, they all make sure I take them. (Female, 30s)

Successful health management experiences were often tied to more robust levels of social and physical capital that promoted access to care, insurance, and pharmacy benefits. Critically important social support from relatives or other trusted persons arose as valuable for health promotion as well. In the context of stigma related to substance use, injecting behaviors and HIV risk, participants often expressed a tension between privacy and disclosure, generally preferring to keep their behaviors personal but also selectively seeking safe spaces for disclosing issues around substance use. For participants who had a provider or family member with whom they could openly disclose their substance use and health concerns, there were tangible benefits that optimized their healthcare that may also support PrEP care:

I go to them monthly. I have high blood pressure. I get, that's why I get high blood pressure medicine. She's a good doctor, yeah, they treat you well. Well, I sort of, I know her too. I grew up with her kids. I know who she is, so I did feel comfortable with her. (Male, 30s)

Um, um, my, well, my doctor is, um, um, one of my good friends. I've been friends with her pretty much all my life. She lived next to me when I was seven or eight. Now she's a nurse practitioner. So she knows what I do. (Female, 30s)

I have an older sister that lives here in the community and things, and she's very supportive because she's been in the healthcare profession. So if I was to have issues, as far as getting somewhere transportation or anything like that, you know, well, I'm there for you, she'll take me and, you know, like pick up my medication or anything like that. (Male, 50s)

DISCUSSION

This study employed qualitative methodologies guided by PRISM to identify the salient personal, social, environmental, and structural barriers and supports for PrEP uptake among rural PWID, with the goal of informing PrEP intervention efforts tailored for this population. Interview narratives with PWID attending rurally located SSPs captured the lived experiences and engagement of individuals in these programs, and in many cases documented long-standing histories of addiction, significant burdens of substance use disorder, multiple health complications, scarce economic opportunities, and loss of community due to multi-layered experiences of stigma and discrimination. Despite these challenges, however, participants also expressed significant resilience and strength, intentionality, and motivation to engage in HIV prevention.

We found a pervasive gap in locally available HIV information; for all intents and purposes messaging about risk, transmission and prevention was very limited in these rural communities. Consequently, perceptions of risk were generally modest and PrEP awareness was minimal among the PWID we interviewed. We did not find systematic differences in HIV knowledge or risk perception by participant age or gender. Given this very limited exposure to the topic, it is not surprising that some individuals expressed uncertainty about PrEP uptake; to our knowledge there has been no prior systematic effort to examine key components of PrEP acceptability in this population, which is often needed when implementing new healthcare interventions (46). In this regard, Biello et al. found that initiatives to educate prospective PrEP users about the medications and about individual HIV risk would provide an essential mechanism to support PrEP, particularly in areas in which there is little existing knowledge about PrEP (23). Importantly, Furukawa et al. noted that adapting non-stigmatizing communication material that is appropriate for the population at risk of HIV is crucial for its acceptance (49). Given the dearth of PrEP educational materials currently designed for PWID, this would appear to be critically important to pursue. Educational efforts to create awareness and recalibrate perceptions of risk, incorporating specific discussion of high-risk situations may help to overcome uncertainty in gauging personal risk and managing prevention.

Our findings clearly demonstrated pervasive stigma and social exclusion that impacts rural PWID, in some cases undermining the traditionally close social bonds in rural communities, and effectively removing PWID from the protections of community membership. In particular, participants noted extensive enacted stigma from members of the law enforcement community involving policing practices that targeted them for enhanced surveillance. This was especially common among males that we interviewed, who tended to express enhanced concern about law enforcement scrutiny when compared to their female counterparts, tied to their lived histories of incarceration. With respect to law enforcement in particular, robust research has documented the harmful associations of harsh policing practices and increased risk for HIV among PWID (47, 48); this appears to be an especially salient concern in small rural communities where individuals are both well-known to and readily identifiable by police. Consistent with other recent research (37, 50, 51), participants of all ages and genders reported experiences of enacted stigma and dignity attacks in multiple settings, which they associated with reduced engagement with healthcare and

treatment. As noted by Walters et al. (52), pervasive social exclusion is likely to play a large role in inequitable access to PrEP. Our findings resonate with recent research that has identified *exclusion from safety* as a driver of risk in marginalized populations (53) resulting from overt surveillance and discriminatory practices.

Participants concerns about scrutiny and stigma based on their background experiences of social exclusion had a strong connection to their expressed HIV prevention attitudes. We found that stigma related to HIV arose as a direct concern for PrEP uptake, with several participants reflecting that privacy issues would impact their preferences for education, prescribing and monitoring of PrEP. Most expressed a preference for one-on-one, and in-person PrEP education for privacy reasons and were enthusiastic about PrEP integration in the SSPs. These findings align with Allen et al. (21), who demonstrated that integration of PrEP services into venues that PWID already access would serve as a major support for communities with little knowledge of or access to PrEP. Among our sample, SSPs were widely considered safe spaces and trusted locations to receive services, and individuals expressed comfort and security attending these programs. Integration of PrEP care into existing SSPs would represent a structural expansion of the current service model at point of care, essentially creating an enabling environment for HIV prevention (35) and providing a seamless pathway for entry to PrEP care (54).

Strengthening and expanding the care system in rural SSPs to support PrEP services will require attention to adequately resourcing these locations. As observed in the present study, many rural PWID experience resource constraints, or limited physical capital. Conceptualized by White and Cloud (55), physical capital consists of the resources available to fulfill a person's basic needs, including healthcare, financial resources, clothing, food, safe shelter, and transportation. In this sample, physical capital barriers to PrEP uptake were common, but were mitigated to some extent by the presence of family housing and nearly universal health insurance coverage due to Kentucky's Medicaid expansion. Nevertheless, economic resources were extremely scarce, which deeply impacted access to reliable transportation and ability to pay for consistent phone or internet service, which allows people to connect with needed healthcare in an ongoing way.

Among the most notable supports for PrEP care were universal health insurance coverage, consistent pharmacy access, and histories of successful health management for other conditions. Kentucky's position as a southern Medicaid expansion state has afforded greater insurance and prescription benefit coverage among PWID, which will be critical for expansion of PrEP services and effectively reduced SSP clients' concerns about costs of PrEP medication. Removal of this structural barrier has contributed heavily to clients' experience of expanded access to healthcare and treatment services; unfortunately, we documented that many care episodes were adversely impacted by stigma and noted that clients reported improved engagement in care when providers were known, trusted, and empathetic, which supported open, non-judgmental communication. This finding is consistent with prior research demonstrating the importance of a robust therapeutic alliance for optimal HIV care planning (56) and fostering engagement and patient agency and activation in the care process (57). In this regard, recent research on HCV treatment and cure among PWID has documented important non-clinical impacts of treatment for health and wellbeing, including increased agency, confidence, and empowerment [(58)], which resonates with our finding that episodes of successful health management appear poised to support increased readiness for PrEP uptake.

LIMITATIONS

This study is limited by a number of factors, including that it is heavily context-dependent, providing a snapshot of PWID's lived experiences in rural Kentucky communities that are both economically distressed and in the midst of a longstanding substance use epidemic, and operating in a policy environment that may be unique when comparted with communities in other locations. Second, given that interview participants were recruited from SSPs, they are not necessarily inclusive of all PWID in the targeted communities; this group may differ in important ways from PWID who do not utilize community harm reduction services. Finally, these narrative accounts are self-reports, which may be impacted by social desirability, self-presentation, and recall biases to an unknown extent. Assurances of confidentiality and the use of experienced neutral interviewers were employed to mitigate these potential deficiencies in self-report data.

CONCLUSION

Drawing on the critical perspectives of people with lived experience, our findings provide important and actionable information on individual and environmental barriers and facilitators of PrEP uptake among rural PWID at high risk for HIV infection. These data will drive the adaptation and implementation of a client-centered approach to integrated PrEP care within rurally located SSP settings to address unmet needs for PrEP care.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data are in-depth qualitative interview transcripts, which due to their detail, are potentially identifiable. Requests to access the datasets should be directed to hilary.surratt@uky.edu.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

HS designed the study, obtained funding, led the data analysis, and wrote the first draft of the manuscript. HY assisted with data coding and preparation of the manuscript. AA, EG, EN, and TW assisted with data coding, reviewed, and revised the manuscript. All authors have reviewed and approved the final manuscript.

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Cultural Adaptation and Validation of the Urdu Version of the Cognitive Emotion Regulation Questionnaire (CERQ) in Male Patients With Substance Use Disorders (SUDs) in Pakistan

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Background: Adults with substance use disorders (SUDs) often have co-occurring mental health problems. Emotion regulation may play a vital role in mental health problems. The Cognitive Emotion Regulation Questionnaire (CERQ) is a widely used measure for assessing cognitive emotion regulation. However, it has not been used in Pakistan on patients with co-occurring SUDs and mental health issues. The present study aims to translate and adapt the CERQ into the Urdu language and to determine its reliability and convergent validity in a sample of male patients with SUDs in Pakistan.

Method: Participants completed a demographic information form, the CERQ, the Depression, Anxiety, and Stress Scale Short Form [DASS-21)], and the Rosenberg Self-Esteem Scale [RSES)] in Urdu.

Results: Male participants (N = 237) 18–50 years of age (M = 29.8, SD = 8.1) were recruited from four substance use disorder treatment centers and hospitals in Karachi. The reliability of the Urdu version of the CERQ was based on an examination of its internal consistency reliability (Cronbach's α) and test–retest reliability for both the total scale and its subscales. Internal consistency for the CERQ total (α = 0.80) was adequate, as it was for subscales of self-blame, (0.76) acceptance (0.78), rumination (0.72), positive refocusing (0.79), focus on planning (0.89), positive reappraisal (0.81), putting into perspective (0.83), catastrophizing (0.73), and other blame (0.70). The 10–14 day test–retest reliability of the CERQ total score was 0.86. Higher CERQ scores were significantly (ps < 0.001) negatively associated with DASS-21depression (r = –0.24), anxiety (r = –0.23), and stress (r = –0.27) subscales, as well as the DASS-21 total score (r = –0.26) and positively associated with the RSES self-esteem score (r = 0.30).

Conclusion: The Urdu version of the CERQ is a reliable measure for investigating cognitive emotion regulation strategies related to mental health and SUDs in Pakistan.

Keywords: cognitive emotion regulation, self-esteem, substance use, depression, anxiety, stress

INTRODUCTION

In the past two decades, research on the construct of emotion regulation (ER) has grown rapidly. ER is defined as strategies to maintain, increase, or suppress a current affective state and includes the ability to regulate emotions and physiological changes to respond to a situation adequately (1). ER aims to analyze, modify, and control emotional responses, help regulate positive and negative emotions and assess any emotion's severity and extent (2, 3). Researchers have studied ER in different fields, including its application with individuals suffering from various psychopathologies [e.g., (4)].

Disruptions in the ability to regulate emotions have been linked to various psychopathologies, including anxiety and depression (5). Numerous research efforts have identified that ER may become dysfunctional when positive emotions do not balance the regulation of painful emotions. This lack of balance can lead to an inability to cope with unpleasant and persistent negative emotional states (6). These unpleasant and ongoing conditions are disturbing and may easily trigger the development of anxious and depressive symptoms (7). Individuals might try to regulate these undesired states and symptoms with psychoactive substance use and other impulsive and risky behaviors (i.e., non-suicidal self-harm injuries) (8). This emotional dysregulation may impair emotion recognition, which may further increase the risk of impulsive and psychoactive-substance-using behaviors, leading to suicidal ideation and behaviors (9). Moreover, several studies have pointed out that alexithymia (the inability to recognize or describe one's own emotions) may be a risk factor for suicide and self-harm in individuals with substance use disorders (SUDs) (10, 11).

Individuals using maladaptive cognitive emotion regulation strategies (CERs) are prone to risky behavior, including substance use disorder (12). Researchers have found that the lack of ER strategies often leads to risky behaviors and ultimately escalates negative emotions (13). For instance, Froushani and Akrami (14) found that a low ER level resulting from the inability to cope effectively and manage emotions plays a role in the onset of drug use. Shahzad et al. (15) reported that in a sample of male patients with SUDs, emotion regulation strategies predict depression.

Similarly, previous findings have indicated a strong association between mental health issues like anxiety, depression, aggression, and psychological distress with low adaptive coping strategies and the excessive utilization of maladaptive strategies (4, 16). There has been a growing interest in having mental health professionals add emotion regulation as a component of psychotherapy [e.g., (17)]. Garnefski et al. (18) have conceptualized cognitive emotion regulation (CER) as a "conscious, cognitive way of handling the intake of emotionally arousing information." They conceptualized different CER strategies, which include; self-blame, other-blame, rumination, catastrophizing, putting into perspective, positive refocusing, positive reappraisal, acceptance, and planning (18), and have developed the cognitive emotion regulation questionnaire (CERQ) to measure these aspects of CER. Since its development, the CERQ has become a widely used measure for assessing cognitive emotion regulation.

Based on the published literature, CER may have a significant role in mental health and SUDs. It is an essential constituent in assessing patients in clinical research and practice. Researchers have asserted that clinicians must have a reliable and valid tool that can be used in different languages and cultures (19). This goal can be achieved through translating and validating a measure from the original language into other languages (20).

Since its development, the CERQ has been translated into several different languages, including Indonesian (21), Arabic (22), Spanish (23), German (24), Turkish (25), Persian (26), Chinese (27), and French (28). Subsequent research has shown that these translations have excellent psychometric properties, including good reliability and validity. However, studies have yet to examine CERQ reliability and convergent validity in a sample of patients with SUDs. The CERQ has also yet to be translated and adapted into Urdu. In line with previous studies, the present study examined the reliability and convergent validity of the CERQ administered in Urdu, in a sample of adult males with SUD in Pakistan. Construct validity of the CERQ was assessed by investigating its relationships with self-report measures of depression, anxiety and stress, and self-esteem.

MATERIALS AND METHODS

Ethical approval for the study was granted by the Departmental Ethical Review Committee, Institute of Clinical Psychology, University of Karachi, Pakistan. The concerned authorities of substance use treatment and rehabilitation centers/hospitals (i.e., Addicare Center for Treatment for Substance Use and Mental Health Problems, Alhaq Medical Center, Nai Zindagi Welfare Trust, and Parvarish Recovery Center) were approached and provided permission for the study to be conducted in their centers/hospitals. Data were collected from 01 June to 30 December 2019.

Participants

The present study recruited only male patients with a SUD. Although reports of psychoactive substance use among females are also a growing concern in Pakistan, access to this population is challenging due to the extreme stigma and discrimination associated with substance use in females in Pakistan and the fear and shame associated with this problem among women.

Adult male patients diagnosed with SUD were recruited using a purposive sampling technique. A total of 300 participants were initially approached to participate in this study: 5 refused to participate, and 58 did not meet the criteria to participate in the study, leaving a sample of 237 participants. Inclusion criteria were a SUD diagnosis, completion of a minimum of 3 weeks in treatment, detoxification completion, clinically stable, and ability to respond. Exclusion criteria included being unable to comprehend the instructions provided to complete the research questionnaires and being unable to read and write.

Translation Process

The authors obtained permission to translate and adapt the CERQ via email from its copyright owners.

Expert Panel

Experts were selected according to the guidelines provided by the International Test Commission (29). These guidelines state that experts should have sufficient knowledge of both the source and target languages, both source and target cultures, the test content, and general testing principles. All four experts were bilingual with prior experience with translation, and all held a Ph.D. in clinical psychology. Two took part as experts for forward and two for backward translation.

Forward Translation

The instrument was first independently translated into Urdu by the two forward translators. To independently translate the original English CERQ into Urdu, the translators were provided detailed information about the scale's content and the study's objectives, and the sample to be recruited. After independent translation into Urdu, the directions, items, and format of the two different Urdu versions were compared with each other and with the original English version of the scale by the expert panel. The expert panel critically evaluated the translated version to resolve any contradictions and ambiguities in the items. Items of both translations that retained Pakistani culture's conceptual, linguistic, and cultural aspects were merged into a single draft. Substitutes recommended by the experts were also taken into consideration. All the items were retained, and no items were removed in the forward translation process.

Backward Translation

The final forward-translated version was then given to two expert translators for backward translation. These two individuals were not involved in the forward translation and were completely blind to the original version of the CERQ to minimize any bias in back-translation. These two translators independently translated the Urdu version back into English. Each item from the backward translations was analyzed and compared with the original English version of CERQ. Items after backward translation that did not retain the initial concepts were modified and rephrased by the translators. All comments given by the experts were transcribed. After a thorough evaluation of this preliminary version, a final version of the Urdu CERQ was prepared. It was then initially piloted on 30 individuals to determine feasibility. No further revisions were necessary, and the Urdu CERQ was determined to be ready to administer and test.

Measures

Participants completed the Urdu translated version of CERQ, the Depression, Anxiety, and Stress Scale Short Form [DASS-21; (30)], and the Self-Esteem Scale [RSES; (31)]. The DASS-21 and the RSES had previously been translated into Urdu.

Cognitive Emotion Regulation Questionnaire (CERQ)

The CERQ has 36-items, including nine conceptually distinct subscales (32). The nine subscales of the CERQ are self-blame, acceptance, rumination, positive refocusing, focus on planning, positive reappraisal, putting into perspective, catastrophizing, and other blame. Each subscale consists of 4 items, each stating what someone thinks after experiencing threatening or stressful life events. The items are measured on a 5-point Likert-type scale ranging from 1("almost never") to 5 ("almost always"). A CERQ total score is obtained by summing the scores on all 36 items (possible range: 36–180). Subscale scores are obtained by summing the scores of the particular subscale (possible range for each subscale: 4 to 20). Previous research in an English-speaking sample has shown that all subscales have good internal consistencies ranging from 0.68 to 0.86 (32).

Depression Anxiety and Stress Scale, Short Form (DASS-21)

The DASS-21 is a self-report short form of the 42-item DASS (30). It is comprised of three subscales, namely, depression, anxiety, and stress. It contains 21 items measured on a 4-point scale in which "not at all" is scored as 0 and "all the time" as 3.Sample items are: "I couldn't seem to get any enjoyment out of the things I did," "I perspired noticeably (e.g., hands sweaty) in the absence of high temperatures or physical exertion," and "I found myself in situations that made me so anxious I was most relieved when they ended." DASS-21 total score can range from minimum 0 to maximum 63, while scores on each subscale can range from 0 to 21. Reliability studies of the Urdu version of the DASS indicate excellent internal consistency reliability for the total score (Cronbach's $\alpha = 0.93$) and respectable internal consistency reliabilities for the subscales: depression (0.84), anxiety (0.86), and stress (0.83), respectively (33).

The Rosenberg Self Esteem Scale (RSES)

The RSES was developed by Rosenberg (31). It contains 10 self-report 4-point Likert-type items to which respondents indicate "strongly disagree" to "strongly agree." Some items are reverse-scored so that the total score scale ranges from 0 to 30, inclusive, with higher scores indicating higher self-esteem. An Urdu version of the RSES has good internal consistency ($\alpha = 0.77$) and a 4-week test re-test correlation coefficient of 0.81 (34).

Procedure

Before enrollment in the study, potential participants were provided with an information sheet that shared the study and informed consent procedures. This sheet included the study's objective, voluntary participation, nature of confidentiality, risk, and benefits, and researcher contact details for possible contact after study completion. Data were only collected from those patients who were deemed stable. Participants completed a patient information form at the start of the study. Personal information was obtained regarding age, gender, number of siblings, education, residential area, family structure, number of family members, family income and number of earning members, drug of addiction, history, and the onset of the problem. Researchers ensured test conditions were similar for the instructions and administration of measures at their respective treatment and rehabilitation centers. Out of 237 participants, our Urdu version of the CERQ was re-administered to 47 participants, with a 10–14 days gap. The scores obtained from the same participants on the two different administrations of

the test could then be compared be correlated to assess test–retest reliability.

Statistical Analyses

Cronbach's α was used to estimate the internal consistency reliability of the CERQ and its subscales. In contrast, simple Pearson product–moment correlations were used to assess test–retest reliability, calculated for the 47 participants who were re-administered the CERQ. Convergent validity of the CERQ was determined by examining the simple Pearson product-moment correlations of the CERQ total score and subscale scores with the DASS-21 total and subscale scores and with the RSES score. All statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS, V-23.0).

RESULTS

Participant Characteristics

Male patients ($N = 237$) 18–50 years of age (M = 29.8, SD = 8.1) were recruited from different substance use treatment centers and hospitals in Karachi, Pakistan. Regarding marital status, 57.4% reported they were single, 40.9% married, and 1.7% divorced. Their mean years of education completed was (M = 5.3, SD = 5.5) with a monthly income in PKR (M = 24677.2, SD = 31340.5). Regarding work status, 43% were employed, 22.4% were on daily wages and worked as laborers, 14.8% had their own business, and 19.8% were unemployed. In terms of living arrangements, 44.3% lived in a nuclear family setup, and 55.7% were in a joint family setup. Regarding the type of substance use, 44% reported using heroin, 15.6% used cannabis, and 32.9% reported using multiple psychoactive substances. Regarding using psychoactive substances, 32.1% reported such use due to family-related issues (i.e., conflicts). A total of 27.8% reported started using psychoactive substances for experimentation, 27% reported use due to personal psychological issues, and 13.1% reported use due to friends using. Regarding substance use history in their family, 39.2% reported use by their immediate family members. When asked about family history of substance use, 39.2% reported that at least one immediate family member uses drugs.

Table 1 presents descriptive statistics for all self-report measures, including subscales.

CERQ Reliability

Our Urdu version of CERQ had good to excellent internal consistency reliability for the total score and subscale scores (see the left-hand section of **Table 2**), with Cronbach's $\alpha = 0.80$ for the total score and subscale reliabilities ranging from $\alpha = 0.70$ (for other blame) to $\alpha = 0.89$ (for focus on planning).

The left-hand section of **Table 2** also lists the test–retest reliabilities for the CERQ total and subscale scores. Of the ten correlations, seven were equal to or >0.9, and the lowest value was 0.76 (for catastrophizing).

TABLE 1 | Descriptive statistics for the Cognitive Emotion Regulation Questionnaire (CERQ) and its subscales, the Depression Anxiety and Stress Scale, Short Form (DASS-21) and its subscales, and the Rosenberg Self-esteem Scale (RSES) ($N = 237$).

Measures	*Min*	*Max*	*M*	*SD*
CERQ Total	112	172	130.2	10.0
Self-blame	11	20	17.8	1.9
Acceptance	15	20	18.5	1.5
Rumination	15	20	18.4	1.5
Positive refocusing	5	20	9.5	2.2
Focus on planning	4	18	9.8	2.7
Positive reappraisal	5	18	9.4	2.3
Putting into perspective	4	16	9.3	2.0
Catastrophizing	15	20	18.5	1.5
Other blame	15	20	18.0	1.5
DASS-21 Total	3	72	43.1	14.3
Depression	0	27	14.6	5.2
Anxiety	0	25	14.0	5.3
Stress	1	23	14.4	4.6
RSES Self-esteem	10	30	15.1	4.9

M, mean; SD, standard deviation; CERQ, Cognitive Emotion Regulation Questionnaire; DASS-21, Depression Anxiety and Stress Scale; Short Form; RSES, Rosenberg Self Esteem Scale. The CERQ total score has a possible range of 36–180, inclusive, while the CERQ subscale scores have a possible range of 4–20, inclusive. The DASS-21 total score has a possible range of 0–63, while the DASS-21 subscale scores have a possible range of 0 to 21. The RSES score has a possible range of 0–30, inclusive.

CERQ Convergent Validity

Not listed in **Table 2** are the internal consistency reliabilities for the DASS-21 total (Cronbach's $\alpha = 0.95$) and the RSES (Cronbach $\alpha = 0.91$), which were calculated to assess the reliabilities of the convergent validity measures as the indices of reliability of the two respective measures whose correlation is examined sets the lower bound for a validity coefficient. As such, if the reliabilities of the DASS-21 and the RSES were deficient, the convergent validity coefficients would have been adversely impacted, something which did not occur here.

The simple Pearson product-moment correlations of the CERQ total and subscales scores with the DASS-21 total and subscale scores and the RSES score are presented in the right-hand section of **Table 2**. Results for the CERQ total score indicated that it was significantly negatively associated with the DASS-21 total score and the depression, anxiety, and stress subscale scores ($p < 0.001$) and positively associated with self-esteem ($p < 0.001$). There was a clear pattern to the correlations of the CERQ subscale scores with the DASS-21 total and subscale scores and the RSES score, with the CERQ subscales that measure positive characteristics (e.g., focus of planning) showing significant negative associations with the DASS-21 total and subscale scores, and a positive association with the RSES score.

DISCUSSION

The aims and objectives of this study were: (1) to develop a culturally sound Urdu version of CERQ; and to investigate (2)

TABLE 2 | Internal consistency reliabilities (Cronbach's α) and 10–14 day test–retest reliabilities (Pearson Product-Moment Correlations) of the CERQ total and subscale scores, and Pearson Product-Moment Correlations of the CERQ scores with the DASS-21 total and subscale scores and the Rosenberg Self-Esteem Scale ($N = 47$ for test–retest reliability; $N = 237$ otherwise).

	Reliability		Convergent validity				
			DASS-21				RSES
Measures	**α**	**Test-retest**	**Total Score**	**Depression**	**Anxiety**	**Stress**	
N	237	47	237	237	237	237	237
CERQ Total	0.80	0.86	**−0.26**	**−0.24**	**−0.23**	**−0.27**	**0.30**
Self-blame	0.76	0.85	**0.19**	**0.18**	**0.23**	0.12	**0.14**
Acceptance	0.78	0.92	−0.03	−0.04	−0.02	−0.03	−0.01
Rumination	0.72	0.95	−0.11	−0.10	−0.07	**−0.15**	0.10
Positive refocusing	0.79	0.94	**−0.33**	**−0.29**	**−0.35**	**−0.31**	**0.24**
Focus on planning	0.89	0.98	**−0.30**	**−0.26**	**−0.32**	**−0.28**	**0.19**
Positive reappraisal	0.81	0.97	**−0.23**	**−0.25**	**−0.19**	**−0.21**	**0.22**
Putting into perspective	0.83	0.99	**−0.17**	**−0.20**	**−0.14**	**−0.15**	**0.18**
Catastrophizing	0.73	0.76	−0.01	0.010	0.01	−0.04	0.15
Other blame	0.70	0.90	**0.13**	0.122	0.12	**0.13**	0.00

*CERQ, Cognitive Emotion Regulation Questionnaire; DASS-21, Depression Anxiety and Stress Scale, Short Form; RSES, Rosenberg Self Esteem Scale. All test–retest correlations are significant at $p < 0.001$. For the Pearson product-moment correlations (rs) of the CERQ scores with the DASS-21 total and subscale scores and RSES scores, iff $|r| > 0.127$, then r is significant at 0.05, while iff $|r| > 0.212$, then r is significant at $p < 0.001$. The values for those correlations whose $p < 0.05$ are **bolded**.*

the reliability of this Urdu version of the CERQ; and (3) its convergent validity in a sample of male patients with SUD. Convergent validity was examined regarding the relationship of the CERQ total and subscale scores with depression, anxiety, and stress and a measure of self-esteem. No normative data on these measures are available in Pakistan, but the examination of the means in relation to their respective range of scores, as well as their respective standard deviations, would suggest reasonable estimates of DASS-21 and RSES. The overall findings of this study support the strong psychometric properties of the Urdu translated version of CERQ.

The reliability and convergent validity of the Urdu version of the CERQ in a sample of adult males with SUDs would suggest that this translated measure could be used to better understand the CER strategies in this population. This better understanding of cognitive and emotional regulation may then aid in designing and implementing interventions to improve people's coping strategies with substance use disorder. Better interventions for cognitive and emotional regulation may, in turn, help improve treatment adherence, maintain a drug-free status, and overall recovery. Psycho-education of patients with SUDs, their families, and significant others about substance use could also help reduce the stigma and discrimination that creates barriers to recovery.

The present findings show an inverse relationship of CER strategies with depression, anxiety, and stress and a direct relationship with self-esteem. In the context of a substance use disorder, CER strategies, specifically maladaptive strategies, can significantly impair psychosocial functioning. So, it is vital to understand how and when these maladaptive strategies can be detrimental and intervene to overcome these problems. According to a model from Gross (35), emotion regulation plays a crucial role in health outcomes. According to Compare et al. (36), people's strategies to regulate their negative emotions are strongly associated with mental health problems such as depression; emotion dysregulation is more common in depression that impairs an individual's social skills and capacity to identify emotions and quality of life. This study's findings are consistent with previous studies, which found that inappropriate emotion regulation is an integral part of developing and maintaining depression and anxiety disorders (37, 38). Other researchers found that depression is linked with impaired cognitive control, such as difficulty accepting and processing negative material (39). There is research evidence to support this study's findings regarding the role of self-esteem in mental health outcomes (40). Results suggest that low self-esteem can lead to a lack of development and a tendency toward drugs or alcohol consumption (41). Other researchers also found the role of environmental stressors in reducing a person's well-being. Low self-esteem can contribute to various social problems like substance use, and it often plays a vital role in this regard (42).

Individuals use emotion regulation strategies to manage and reduce the consequences of the stressors (43, 44). Some research suggests that reliance on emotion-focused coping (e.g., worry, self-blame) is related to the risk of experiencing mental health issues such as anxiety, depressive symptoms, and drug use (45, 46). A study examining the influence of emotion regulation strategies in depression among male patients with SUDs found that emotion regulation strategies such as affect suppression significantly predicted depression (15). Another study of male patients treated for SUDs concluded that patients with SUDs showed a stronger tendency to use emotion-focused coping efforts, including self-criticism and problem avoidance when facing problems than patients with severe mental illness

(47). Thus, patients with SUDs may be using avoidance and disengagement strategies to cope with the difficult situation in an unsuccessful way, which could negatively interfere with treatment adherence and treatment outcome. The relationship between emotion regulation strategies and SUD is necessary for the study reported here. Individuals with adaptive coping strategies respond to challenging situations to reduce the risk of substance use. Those with emotion-focused coping strategies may be less equipped to deal with stressful life situations, leading to higher chances of using drugs. Such a conclusion is consistent with Capella and associates (48) findings that male patients with SUDs who rely on avoidance coping strategies are likely to use drugs. Thus, perhaps individuals depending on emotion-focused coping strategies use drugs to deal with negative emotions and stress.

Limitations

The present study has certain limitations related to the study design. The sample was one of convenience, and data were collected at a single time. However, the relationship of cognitive emotion regulation strategies with depression, anxiety, stress, and self-esteem could operate differently over time. Furthermore, the sample only included male patients receiving treatment for SUD. Thus, generalizability is limited to male patients without a SUD, female patients with or with a SUD, or the non-patient general population. Future research may wish to include a more diverse sample, including non-clinical samples, to understand the role of emotion regulation in improving well-being and mental health outcomes in males and females without a SUD. Future research may also attempt to disentangle the role of emotional regulation as a possible mediator between mental health issues and substance use disorder.

CONCLUSIONS

Existing literature related to cognitive emotion regulation strategies indicates a strong link between cognitive emotion regulation with mental health problems and self-esteem. The present study showed that the Urdu version of the CERQ would be a reliable measure for patients with SUD. Using this measure may help us fill the gap in understanding the emotion regulation strategies and implementing evidence-based practices (EBPs) while linking it with the client's specific problems to improve treatment outcomes. In addition, the Urdu version of the CERQ may be helpful in the identification of adaptive and maladaptive strategies that may constitute the basis for preventive or treatment interventions specifically for patients with SUD aimed at enhancing their well-being.

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 study involving human participants were reviewed and approved by Departmental Ethical Review Committee, Institute of Clinical Psychology, University of Karachi, Pakistan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS main researcher, design of the research, wrote part of the manuscript, and responsible for the sample selection, data collection, and data analysis. NBa wrote the introduction and discussion. NBe provided data collection, wrote part of the manuscript, and provided statistical analysis. HJ provided manuscript reviews, edits, corrections, and amendments. All authors participated and approved the study design, contributed to manuscript revision, read, and approved the submitted version.

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Experiences Using a Multidisciplinary Model for Treating Injection Drug Use Associated Infections: A Qualitative Study

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Background: Over the past two decades, the United States has experienced a dramatic increase in the rate of injection drug use, injection associated infections, and overdose mortality. A hospital-based program for treating opioid use disorder in people who inject drugs presenting with invasive infections was initiated at an academic tertiary care center in 2020. The goal of this program was to improve care outcomes, enhance patient experiences, and facilitate transition from the hospital to longer term addiction care. The purpose of this study was to interview two cohorts of patients, those admitted before vs. after initiation of this program, to understand the program's impact on care from the patient's perspective and explore ways in which the program could be improved.

Methods: Thirty patients admitted to the hospital with infectious complications of injection drug use were interviewed using a semi-structured format. Interviews were transcribed and coded. Emergent themes were reported. Limited descriptive statistics were reported based on chart review.

Results: Thirty interviews were completed; 16 participants were part of the program (admitted after program implementation) while 14 were not participants (admitted prior to implementation). Common themes associated with hospitalization included inadequate pain control, access to medications for opioid use disorder (MOUD), loss of freedom, stigma from healthcare personnel, and benefits of having an interprofessional team. Participants in the program were more likely to report adequate pain control and access to MOUD and many cited benefits from receiving care from an interprofessional team.

Conclusions: Patients with opioid use disorder admitted with injection related infections reported improved experiences when receiving care from an interprofessional team focused on their addiction. However, perceived stigma from healthcare personnel and loss of freedom related to hospitalization were continued barriers to care before and after implementation of this program.

Keywords: persons who inject drugs, opioid use disorder, substance use disorder, AMA discharge, medications for opioid use disorder

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INTRODUCTION

Over the past two decades, the United States (U.S.) has experienced a dramatic increase in misuse of both prescription and non-prescription opioids. A three-phase epidemic, which started with prescription opioids and progressed to illicit heroin and then fentanyl, has now culminated in a dramatic rise in injection drug use (IDU) across the U.S. (1). In the last year, overdose deaths have rose to over 100,000, with over 60% involving synthetic opioids (2). Complications related to IDU have also increased (3). People who inject drugs face higher rates of serious bacterial, fungal and viral infections (specifically human immunodeficiency virus and viral hepatitis) (4–7).

A growing body of evidence suggests that hospital outcomes for infectious complications of IDU are improved when people who inject opioids are treated with medications for opioid use disorder (MOUD) (8–11). In patients presenting with OUD, MOUD have been associated with a decrease in all-cause mortality, overdose events, and need for acute care related to opioid use (12, 13). However, initiation of MOUD may not be enough to improve outcomes; patients not remaining on these medications lose the survival benefit previously imparted by them (14, 15). Unfortunately, many patients with OUD who are discharged from the hospital struggle to find access to MOUD. Large organizations, including the National Academies of Sciences, Engineering, and Medicine, have called for more resources to increase MOUD prescribing and the development of programs to link patients to community-based treatment (16). A continuum of care model, similar to that used for patients living with HIV, has been proposed with the goal of transitioning patients along a care pathway, from identification, to stabilization, and linkage to long-term OUD management (17, 18).

The Washington University School of Medicine bridge-to-health program was initiated as a Centers for Disease Control and Prevention (CDC) funded program for treating opioid use disorder (OUD) in people who inject drugs (PWID) presenting to the hospital with invasive infections associated with injection drug use (19). Patients that are prospectively identified by infectious disease physicians, hospitalists, and social workers can be enrolled in the program, which provides access to a peer recovery coach, a dedicated program social worker, a clinical counselor, and physicians who can follow-up post discharge. Participants receive free MOUD, vaccinations to prevent injection associated infections (e.g., hepatitis A and B), and linkage to post-discharge infectious diseases care that can provide oral antibiotics for patients who discharge prior to completion of IV antibiotics, pre-exposure prophylaxis for HIV, and treatment for hepatitis C infection (when appropriate). If patients continue using injection drugs, they are also offered a harm reduction kit that includes wound care supplies, alcohol swabs, and educational materials. All patients are offered take-home naloxone. Patient enrollment in the program is voluntary and requires no long-term commitment. Upon hospital discharge, patients are followed in a bridge-to-health clinic, either in-person or via telemedicine, and continue to receive intensive social work and peer recovery resources for 90 days after discharge, followed by a handoff to community providers for continuation of their addiction care. The goal of this program is to provide supportive services for PWID presenting with injection related infections, decrease readmissions, and improve retention in outpatient infectious diseases and substance use disorder care (19).

The purpose of this study was to interview patients admitted to the hospital with a serious injection-related bacterial or fungal infection before and after initiation of the multidisciplinary bridge-to-health program, to understand its impact from the patient's perspective and explore ways in which the program could be improved.

METHODS

From April to October 2020, we conducted 30 semi-structured interviews with patients admitted to a 1400-bed academic, tertiary hospital in St. Louis, Missouri, for invasive infections related to IDU. Adults, over the age of 18 years, hospitalized for a serious IDU-related infection (i.e., endocarditis, osteomyelitis, septic arthritis, epidural abscess or *S. aureus* bacteremia) from January 2018 until October 2020 were eligible for participation. There were no exclusion criteria. Eligible patients were recruited, via phone call, from a cohort of patients who were being treated and followed in an infectious disease clinic for infections related to their drug use. Interviewees provided informed verbal consent and were given a $20 gift card for their participation. This study was approved by the Washington University Human Research Protection Office.

Each patient who consented to partake in this study participated in a phone interview (ranging from 10 to 40 minutes) with one of three research assistants (two male, one female) trained in qualitative interviewing. These research assistants were peer recovery coaches for the bridge-to-health program who often developed a rapport with patients through the context of the program. Topics included (1) nature of the patient's hospital experience and interactions with staff; (2) desire to leave against medical advice (AMA); (3) motivation and resources for recovery from OUD (e.g., MOUD, social support, abstinence-based groups); (4) self-management of past skin or minor infections; (5) knowledge and use of practices to prevent infection (e.g., HIV pre-exposure prophylaxis, hepatitis vaccination, use of sterile needles); and (6) feedback to healthcare personnel on how best to support patients with OUD. Questions targeted the experiences patients had while hospitalized and no questions specifically asked about patient experiences in the bridge-to-health program. Study members recorded and transcribed the interviews. Quantitative data were abstracted from the medical record with permission from the participants.

Interview transcripts were coded thematically using NVivo qualitative research software (NVivo 12, QSR International). A constructivist grounded theory approach was taken, with the goal of exploring the experiences of two cohorts of patients admitted to the hospital with OUD: those admitted before and those admitted after the initiation of the bridge-to-health program (20, 21). Reviewers were blinded to whether the

study participants were engaged in the program. NN, an infectious disease fellow, and EG, a pre-medical student with a background in qualitative research, independently reviewed each audio recording and transcript. The reviewers corrected for transcription errors or omissions. Codes were generated inductively using an open coding process with active comparison between coders. Axial coding was used to generate a codebook, with iterative modification of the codebook based on re-review of the transcripts. These two researchers then independently coded all 30 transcripts and discussed any coding ambiguities or discrepancies. Codes were diagramed according to emergent themes and were analyzed based on time period, specifically pre- vs. post-implementation of the bridge-to-health program. Illustrative quotes were extracted to facilitate presentation of the data. All methods are reported according to established best practices (22).

RESULTS

Thirty study participants were interviewed about their experiences being hospitalized for IDU-related bacterial or fungal infections. Just under half ($N = 14$) of the participants were hospitalized prior to initiation of the bridge-to-health program (which started in February 2020). Most participants ($N = 18$; 60%) were men. The average participant age was 41.5 years old (SD $\pm$ 11.4). The average length of stay was 25.5 days (SD $\pm$ 21.3). Nine patients left AMA prior to completion of their hospital care (6 in the post intervention group). Nineteen participants had an addiction medicine consult, with fewer consults received during the preintervention period (5/14) compared with the post-intervention period (14/16). Twenty-two participants were prescribed MOUD at discharge (15 prescribed buprenorphine-naloxone, 4 prescribed methadone). The most common IDU-related infections were endocarditis ($N = 13$), osteomyelitis ($N = 10$), and complicated skin and soft tissue infections ($N = 10$) (some patients had more than one infection). Basic demographics are presented in **Table 1**.

TABLE 1 | Participant characteristics.

	Pre $N = 14$	Post $N = 16$	*p*-value
Demographics			
Age (mean, SD)	40.4 (10)	42.5 (11)	
Male	8 (57.1%)	10 (62.5%)	0.77
Female[&]	5 (35.7%)	6 (37.5%)	0.92
Transgender	1 (7.1%)	0 (0%)	0.21
White	4 (28.6%)	8 (50.0%)	0.38
Homeless	2 (14.3%)	3 (18.8%)	0.81
Rural County	3 (21.4%)	4 (25.0%)	0.91
Substance use patterns*			
Heroin	13 (92.9%)	13 (81.3%)	0.34
Fentanyl	5 (35.7%)	10 (62.5%)	0.12
Methamphetamine	3 (21.4%)	5 (31.3%)	0.54
Cocaine	5 (35.7%)	4 (25.0%)	0.52
Inpatient characteristics			
MOUD initiated	8 (57.1%)	14 (87.5%)	0.05
Addiction Medicine consult	5 (35.7%)	14 (87.5%)	<0.01
Reason for admission*			
Infective endocarditis	8 (57.1%)	5 (31.3%)	0.15
Osteoarticular Infection	5 (35.7%)	7 (43.8%)	0.65
Complicated skin and soft tissue Infection	4 (28.6%)	5 (31.3%)	0.87
Comorbidities			
Hepatitis C	9 (64.3%)	10 (62.5%)	0.92
Human Immunodeficiency Virus	1 (7.1%)	2 (13.3%)	0.62

[&] *One female was transgender.*

**Patients may use more than one type of substance, and may have multiple concurrent infectious complications.*

Pain Control and Access to MOUD

When exploring patient narratives, it became clear that many had past traumas associated with inadequate pain control, which frequently impacted how they interacted with their healthcare teams. When discussing a prior hospitalization, a 40–50-year-old White female said, "I felt like they thought, because I was an addict, that I deserved to in the pain I was in." These experiences made patients reluctant to seek care and, when patients did seek care, pain was frequently a source of conflict between them and their hospital team. Even when pain was not a pressing concern, others reported being forced to withdraw without the option of opioid replacement therapies. A 20–30-year-old Black woman, who used opioids and was hospitalized prior to implementation of the bridge-to-health program, explained:

> *"When people come in on drugs with withdrawals and everything, they don't be so quick to get you methadone… I feel that if a person comes in sick with an infection and is on drugs… they should have an option whether they want to be put on any type of methadone or some type of Suboxone [buprenorphine/naloxone] or just want to withdrawal on their own… That's a lot of why I left, because I'm like, 'I'm not going to sit here dope sick.'"*

Several other participants noted that withdrawal and cravings were a significant reason for leaving against the advice of their medical providers.

Participants who were able to participate in the bridge-to-health program often reported improved pain control as compared to prior experiences. For example, when asked about her experience, a 30–40-year-old White female, who used heroin and participated in the program, stated, "they had me on painkillers, because when I was in the hospital, I was in there for surgeries. So, it wasn't so bad. And then when I came down, they gave me Suboxone." Withdrawal and cravings were less likely to be noted following implementation of the program, particularly in those who received addiction medicine consultations. When withdrawal was brought up, it was most often as a discussion

TABLE 2 | Themes and quotes from qualitative interviews.

Theme	Quotes
Pain control and access to MOUD	They should be getting people on Suboxone. They should be setting that stuff up prior before they leave the hospital. - *30–40-year-old White male. Not a participant in bridge-to-health program* The doctors were either awesome or they were very callous. I don't think the doctors respected the fact that I was an addict. And just because you give somebody a prescription and tell them to just take it a certain way, does not mean that individual's capable of it. And one mistake on my part could put a needle back in my arm. And I just feel, after a certain point that they just wanted to... I don't understand why it was so difficult for me to get on, stay on, and be put back on the Suboxone. - *20–30-year-old Black male. Participant in bridge-to-health program*
Stigmatization	I mean, they were all pretty good. It was just that first doctor, like I said, it felt like he was judging me the whole time and I was restricted on some things when other patients I would talk to, or whatever, they had these liberties or whatnot that I didn't have at the time. It was because he knew that I was a user. And I don't think that really should have mattered, whether I do or not. I should have been treated the same regardless. And if I did start abusing something, then, take action. But if I'm not doing anything wrong, who cares? I should be treated the same way as everybody else. - *30–40-year-old White male. Not a participant in bridge-to-health program* I had doctors tell me, "I don't care, leave." They're just gonna go back and use to get high and die ... I'm talking about, this is the doctor telling me that. They're saying to me and that's the person they got to worry about and I'm sitting there like, "What?" We don't need to hear that. - *20–30-year-old Black female. Not a participant in bridge-to-health program*
Loss of freedom	"It'd have been nice if they had somebody come around, maybe once a week, when people were able to get up on their own safely, and be able to go outside and maybe get fresh air… not being able to go outside… that was the hardest part." - *50–60-year-old White male. Not a participant in bridge-to-health program*
Person-centered care	This one nurse, [xxxx] was her name, she would come in, she would make time every night to come in, because I couldn't take a shower for a while ... I couldn't get in the actual shower. But she would make time every night to come help me wash my hair at the sink. She shaved my legs for me. She hand-washed some of my clothes that I had. I mean, it just made me feel really good, and I know she wasn't doing it for recognition. I could tell she was just doing it because she cared, and she liked her job, and I really thought that was amazing. - *40–50-year-old White female. Participant in bridge-to-health program*
Harm reduction	Because they make it hard so where you can't get clean needles. I mean, I never really had a difficult time, because I knew what stores to go to, but I know it is hard for people that don't know where the stores are, because a lot of places won't sell you clean needles unless you are on insulin. Which I mean, I understand they're trying to cut down, but in a way if a person wants to get high, they're going to get high. So why not let them be able to use clean utensils rather than spread disease? Because they're going to do it regardless. - *40–50-year-old White female. Participant in bridge-to-health program*
Benefits of a Multi-disciplinary bridge model	When you're not feeling judged, then you're willing to hear all the options that they have for help, and I really think that's the most important thing is offering the help and options for when they go home. What helped me the most is being able to have somebody like [my recovery coach] that I can talk to about any problems, or cravings, or anything. And then having [my social worker] who I can ask for any help I need help with as far as a case worker. And [my doctor], I mean, she calls me just to check on me. That made me feel so important and special. - *40–50-year-old White female. Participant in bridge-to-health program.*

of prior experiences. One 30-40-year-old Black male, admitted to the hospital following implementation of the bridge-to-health program, reported that his most recent hospital stay "wasn't that bad [because] they treated my withdrawals." Further illustrative quotes for all themes can be found in **Table 2**.

Stigmatization

Many participants described barriers to care beyond pain control, including interpersonal conflicts with clinicians and the experience of judgement or stigma. Even with adequate pain control or the appropriate prescription of MOUD, these additional factors contributed to poor hospital experiences and AMA discharge in some instances. Measures such as direct patient observation (i.e., patient sitters), inability to leave the unit, and searches by security underscored the lack of trust on the part of the clinicians and created a more hostile environment. One 30–40-year-old White male explained, "it felt like [the doctor] was judging me the whole time and I was restricted on some things when other patients I would talk to, or whatever, they had these liberties, or whatnot, that I didn't have at the time."

Some participants had poor interactions with specific members of the healthcare team. One participant recounted how she was denied the antiemetic promethazine by one clinician because it had abuse potential. These episodes reiterated how participants with history of addiction were "othered" in the hospital. A few participants who chose to leave against medical advice cited a single episode of conflict as the inciting factor. When discussing an interaction with a nurse practitioner, a 30–40-year-old White female participant explained:

> *"She ended up coming and wanting to search the room, which was no problem. I had nothing in the room. But I felt like after they searched the room and didn't find anything, and they searched my boyfriend… and didn't find anything… They were still going to make somebody sit there and like babysit me… I just felt kind of disrespected."*

This negative interaction with a single provider led the participant to discharge against medical advice. "That's ultimately why I left," she elaborated, "because of how the nurse practitioner [treated me], I felt like she was singling me out."

When analyzing the experiences of participants before and after initiation of the bridge-to-health program, we found that episodes of stigma and judgement continued to exist post-implementation. However, distinctions emerged, suggesting improved overall experience. Participants in the post-implementation group frequently contrasted negative experiences in other clinical settings with the positive experiences

in the bridge-to-health program. For example, a 40–50-year-old White female described:

> *"My interactions during [this hospitalization], the doctors and the nurses, they were great. I believe they did everything really to their abilities to try and help me, and they did not make me feel like I was any less because I was an addict."*

Despite the program, patients continued to suffer stigmatization, however these concerns were less frequently cited in the cohort of patients admitted to the bridge-to-health program.

Loss of Freedom

Confinement and lack of freedom were frequently brought up by participants, particularly because many patients who use drugs require prolonged hospital stays to receive intravenous antibiotics. A 20–30-year-old Black male who used multiple substances, including opioids and methamphetamine, said, "I had to get used to not being able to come and go as I please. I used to eat what I want, to sleep when I want, or to roll over in bed at two o'clock in the morning and light up a cigarette." For him, even with access to addiction care and peer recovery coaches, loss of freedom made it difficult to stay in the hospital for a prolonged period of time.

The coronavirus disease 2019 (COVID-19) pandemic occurred during the time of this study, resulting in new policies limiting hospital visitors and discouraging patients from leaving their rooms or congregating in common areas. Many participants discussed how changes in hospital policies impacted their care. A 40–50-year-old White female who left AMA explained, "I was fighting drug addiction, but it was being alone. I don't like to be alone. I don't like to be alone… I have abandonment issues." For some of these participants, loss of hospital visits and uncertainty at home complicated their care experience. The theme of COVID-19 and its impact on these patients was recently reported by this team (23).

Unfortunately, the addition of our focused, interdisciplinary team did not alleviate the feeling of isolation and confinement described by many study participants. Though they were thankful for regular visits by peer recovery coaches, there was a profound sense that their freedom was being impacted. Even the fact that their treatment required prolonged hospitalization was enough to make them feel different from other patients. Further, patient obligations often persisted during their hospitalization. One 40–50-year-old White male provided his reasoning for leaving his hospital stay early, "I was ready to get back home because my life was at home and I just got dragged out of it. That's the only reason I left… I missed my family and my family is everything to me." He went on to describe family commitments as the driving force for a discharge against his medical team's advice.

Person-Centered Care

Many participants were quick to highlight the positive aspects of their hospital experiences, particularly physicians or nurses who stood out as exceptional. Even small acts of kindness secured good will and improved the patient's overall view of the staff and healthcare team. A 30–40-year-old White male told the story of coming out of surgery late and missing his dinner tray, "one of the nursing staff members, I can't remember his name, he went and bought me supper down at the cafeteria, with his own personal money." This act left a clear impression on the patient. Another participant, a 20–30-year-old Black male, described how the hospital staff rallied behind him and became a new surrogate support system. "I wanted to be dead... and this woman, this doctor, she helped me through it." He described hospital staff visiting him on their off days and calling to check in on him. Another participant, a 40–50-year-old male, explained how his stay was improved by the excellent nursing staff, "they treated me like family. I was a long way from home and I didn't have no family there with me or nothing. They made that stay better."

Harm Reduction

Participants were asked about existing personal practices to prevent infection and how these could be better supported. Participants often brought up the idea of needle exchanges and safe injection sites, which were not legal in Missouri at the time the study was performed, with the closest needle exchange locations for participants being in neighboring states, such as Illinois. A 40–50-year-old White female explained that her friend lived in a location with safe injection sites: "I can't imagine going somewhere and having somebody help me do it. But at the same time, if there was somebody that could... I think about how my body wouldn't look like it is right now."

Many participants had a strong understanding of safer injection practices; they frequently cited the experience of being admitted with an invasive IDU-related infection as a life-altering event. A 40–50-year-old White woman admitted with endocarditis from injection fentanyl use described her practices regarding injection preparation:

> *"I just do everything as possibly clean as I can. I mean, the water, all of it, just because I know how easy something can happen. And you can think, just like I thought when that happened, that I was doing everything right. I wasn't dirty, but there was something that happened to it. So, yeah. I do things a lot different than I did at that time, a lot cleaner and I won't use a needle more than one time."*

Though many patients expressed understanding of safe injection practices, gaps in understanding regarding medication and vaccine prophylaxis continued to persist, even after the bridge-to-health program initiation. Many participants had little understanding about HIV pre-exposure prophylaxis, which was described by this group elsewhere (24). Further, many had little knowledge about their vaccination status for Hepatitis A and Hepatitis B. Even when records demonstrated that patients were vaccinated during their hospitalization, this frequently was not recalled.

Benefits of a Multi-Disciplinary Bridge Model

Overall, those who were able to participate in the bridge-to-health program were appreciative of the services and frequently cited the benefit of a multidisciplinary approach. A 40–50-year-old White female, who participated stated:

"What helped me the most is being able to have somebody like [my recovery coach] that I can talk to about any problems, or cravings, or anything. And then having [my social worker] who I can ask for any help I need with as far as a case worker. And [my doctor], I mean, she calls me just to check on me. That made me feel so important and special."

Similarly, a 60–70-year-old White male, said, "I have my coach here… I have the methadone clinic, suboxone that I could try. I mean the whole team here is awesome. The doctors, the nurses here, everybody who's involved in my treatment has been awesome."

Participants who were not part of the bridge-to-health program often spoke of their care being disjointed or lacking resources. For example, when a 30–40-year-old White female was asked if she had the resources to quit opioids she responded:

"I do not. Okay. That kind of a question has two different answers to it, because I do have a great support system. My family that will be, and is trying to be, behind me, and all of those different things. But I've never been able to just go through quitting cold turkey on my own."

She elaborated that her struggles with anxiety and not having adequate medications for her addiction have further prevented recovery. Many explained that upon discharge from the hospital they were unable to find stable addiction care or access to medications to treat their addiction. The rate of return to drug use was high in the cohort of patients prior to implementation of the bridge-to-health program.

DISCUSSION

This qualitative analysis was undertaken to explore patient perceptions of a multidisciplinary program to address opioid use disorder (OUD) in the context of hospitalization for a serious injection-related infection. This program (called the bridge-to-health program) was designed to bridge the gap between hospitalization, early discharge and establishment of stable addiction care (19). When comparing interviews with patients admitted before and patients admitted after the initiation of this program, we found several perceived benefits, as well as areas of improvement.

Perhaps the most significant in-hospital change offered by the bridge-to-health program were improvements in access to medications for OUD (MOUD) and overall pain control. Inadequate pain control is often a concern for patients with tolerance to opioids. Patients struggling with addiction have reported being denied analgesia due to concerns that they are "drug-seeking" (25, 26). When analgesia is provided, it may be inadequate due to increased opioid tolerance. Participants in our study had similar concerns. However, following implementation of the bridge-to-health program, we noted fewer concerns about inadequate pain control. In the bridge-to-health cohort, addiction services were part of the program and frequently helped patients and their medical teams navigate acute opioid needs along with initiation of MOUD, when indicated. We found that early involvement of addiction specialists led to one of two outcomes: early initiation of MOUD or recommendation to continue short-acting opioids for pain and delaying initiation of MOUD until the patient was more stable, with a smoother transition off acute opioids and onto MOUD. Lack of addiction medicine consults have been associated with inadequate access to MOUD, even when interprofessional care teams are assembled to improve addiction care (27). Previous data has found that patients with OUD hospitalized with injection-related infections and treated with MOUD have improved outcomes and are less likely to leave AMA (9, 11). Similarly, addiction medicine consults improve patient outcomes (9). These patient narrative data suggest that treating OUD during the hospital stay helped to make the hospital stay less traumatic.

Our results echo other researchers' findings that patient stigmatization by healthcare personnel remains a substantial barrier to improving the care of PWID (10, 28, 29). It is notable that Pollini and colleagues describe an almost identical story to one described above, of a patient having their belongings searched and experiencing inappropriate scrutiny, which ultimately led to an early, patient-directed discharge (30). For many participants in our study, the experience of significant stigma seemingly left the mark of lasting trauma, coloring their interactions with healthcare professionals moving forward. Our qualitative approach adds to the literature by providing several vivid examples, from the patient's perspective, of how stigma harms healthcare interactions and leads patients to leave AMA, or avoid accessing care altogether (31).

However, our findings also identified that reducing stigma can improve healthcare personnel interactions with PWID. In particular, small gestures of goodwill and other displays of person-centered care made a lasting impression on patients and improved the overall patient perception of the hospital experience. At this time, it is unclear what interventions might directly reduce patient-experienced stigma, however we hypothesize that normalization of addiction care through the use of interprofessional teams can help to drive institutional cultural change. Anecdotally, when peer-recovery coaches were added to healthcare teams, all of whom had previously recovered from addiction, important perspectives were added to the care team discussion. Partnering and working with those who have lived experience of the stigmatized condition has been used as a destigmatizing process and may help physicians, nurses, and other health professionals see PWID differently (32, 33).

In our study, feelings of confinement and lack of freedom were common. Hospital policies restricting the movement of PWID, particularly during the COVID-19 pandemic, likely played a role in these perceptions. These concerns were frequently identified among patients who required prolonged inpatient stays for intravenous antibiotics and wound care. These feelings were not alleviated, even with the addition of the bridge-to-health program staff, and were associated with early, patient directed discharge. Others have noted that isolation, loneliness and boredom are associated with difficulty

staying in the hospital to complete long courses of treatment (30). Further research is needed to determine how to best reduce these feelings of confinement, isolation, and boredom among patients.

Much of the bridge-to-health model is centered on harm reduction principles. During initial visits, patients are educated on practices that might have been associated with infection, such as re-using or licking needles, using non-sterile water, and failing to sterilize the skin. While the goal is to help patients avoid injection drug use, those who continue to use are offered education and supplies for infection prevention. While most participants endorsed a basic understanding of infection prevention principles, many cited a lack of support in the surrounding community (e.g., lack of needle-exchanges, lack of safe injection spaces, lack of safe syringe disposal, etc.). Despite education, participants had limited knowledge regarding vaccine and medication strategies as infection prevention. Future efforts will be aimed at expanding education, access and patient support.

Participants who were able to enroll in the bridge-to-health program reported benefits to having a dedicated team that spanned their treatment both inside and outside of the hospital. In this study, more patients who left against their medical team's advice were included in the post intervention analysis. While this might seem curious, it is because, despite leaving against medical advice, these participants remained reachable, often providing reliable contact information and agreeing to follow up before leaving the medical facility. Further, the involvement of a dedicated, interprofessional team focused on co-management of substance use disorder and infections aided discharge discussions, similar to that proposed by other models (34). In contrast, preintervention patients were left without similar options, and many who did discharge against the medical team's advice did so in a less coordinated way, often remaining unreachable or, when reached, declining to discuss their stay.

Interprofessional care teams, similar to the model described in this study, are emerging tools to help combat the opioid epidemic (35). However, some have reported limited success in helping patients to start and remain on medications to treat their opioid use disorder (27). We found that this bridge model, comprising a team that followed the patient in the hospital, and their transition out of it, helped to engage patients and increased retention in follow up care.

Limitations

This study is subject to several important limitations. First, interviews were performed by peer recovery coaches. This increases the risk of acquiescence bias. However, even patients enrolled in the bridge-to-health program seemed uninhibited in sharing negative viewpoints about their hospital care. Further, the interview was very specific in asking about patient's experiences with nurses, staff, etc. It did not ask about patient experiences with the bridge-to-health program or any of its staff. The interviews were not mandatory and played no role on participation in the program. As is typical, sampling bias may have occurred based on those willing to participate in study. Another significant bias is that of recall. Participants in the bridge-to-health program would have been more recently hospitalized, meaning their recall may be clearer, which likely limits some ability to draw comparisons. Some of our patient experiences, particularly those related to confinement and lack of freedom in the hospital, could have been confounded by stricter hospital visitor policies during the COVID-19 pandemic. However, our team also observed this theme among patients hospitalized preceding the pandemic. Finally, the bridge-to-health program grew organically, and quality improvement efforts aimed at improving care for patients admitted with invasive infections related to their addiction had been ongoing before the formal program was established. Some pre-implementation participants may have benefited from services similar to those provided later by the program.

CONCLUSIONS

In the past two decades there has been a dramatic increase in the number of patients presenting to hospitals for complications of injection drug use. Caring for these patients can be difficult, as physicians attempt to balance acute needs with the treatment of the patient's underlying drug use disorder. Further, these patients are at high risk for recidivism and loss to follow up when they transition out of the hospital. A multi-disciplinary model, named the bridge-to-health program, helped to improve the care experiences of patients admitted with infectious complications of their injection drug use. This program improved experiences around pain control, withdrawal, and navigation of care following hospitalization. However, much work still needs to occur when managing stigma and patient loss of freedom (due to hospitalization). This data will inform further quality improvements in the bridge-to-health model and serves to demonstrate its benefits from the patient's own perspective.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are qualitative data that include personal patient interviews. They are stored in a HIPAA compliant manner and as part of consent, we agreed not to share the full interview. Further enquiries can be directed toward the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Washington University in St. Louis Institutional Review Board. The patients/participants provided their recorded verbal informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NN and EG performed analysis of the transcribed interviews and wrote the initial drafts of this manuscript. LM, TH-B, SL, and MD were important in creating the interview questions, evaluating data, and providing critical feedback on the final draft of the manuscript. All authors had access to the data and a role in writing the manuscript.

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Interest in Co-located Reproductive and Sexual Health Services Among Women and Men Receiving Medication for Opioid Use Disorder in an Outpatient Treatment Clinic

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Introduction: Reproductive and sexual health (RSH) are core components of comprehensive care, yet often omitted in addiction treatment. We characterize knowledge of and interest in RSH services and contraceptive method awareness and use in a rural, Appalachian outpatient clinic.

Materials and Methods: Between September 2016 and April 2018, a convenience sample of 225 patients receiving treatment for opioid use disorder at an outpatient buprenorphine/naloxone clinic was collected. Participants completed a cross-sectional RSH survey that included demographics, interest in RSH service integration, contraceptive use, and contraceptive knowledge.

Results: A total of 212 people (126 non-pregnant women, 29 pregnant women, and 57 men) completed the survey of whom 45.8% indicated interest in adding RSH services. Services of interest include regular physical exams (44.8%), STI/STD testing (41.0%), and contraception education and administration (38.2%). There were no significant differences between interest in co-located services between women and men ($P = 0.327$). Current contraceptive use was low (17.9–30.9%) among women and men. Contraceptive method awareness was 43.3% for high efficacy methods and 50.0% for medium efficacy methods. Women and currently pregnant women knew more total, high, and medium efficacy contraceptive method than men ($P = 0.029$).

Discussion: Both women and men in this sample are interested in co-located RSH services. Current contraceptive use was low among participants. Contraceptive knowledge was lower among men compared to women, and generally low. Providing co-located RSH services may facilitate RSH education, contraceptive method uptake, and promote engagement across various RSH domains.

Keywords: opioid use disorder, buprenorphine, contraceptives, STI/STD, rural health

INTRODUCTION

Reproductive health addresses the reproductive processes, functions, and system at all stages of life (e.g., contraceptive counseling) while sexual health is a state of physical, mental, and social well-being in relation to sexuality (e.g., sexual functioning) (1). Although reproductive and sexual health (RSH) is recognized as a key component of holistic medicine, integration of RSH services is lacking in opioid use disorder (OUD) treatment, outside of the attention to the needs of pregnant women with OUD (2). A goal of the Affordable Care Act was to break down the barriers between care systems (3), however, system-level barriers continue, especially for patients receiving OUD treatment (4).

Previous research has shown some interest in women's health services being integrated into addiction treatment facilities (5); however, the degree to which RSH services have been integrated into OUD treatment facilities is low although robust national data are lacking. A recent survey focused on the RSH needs of reproductive-age women assessed opioid treatment programs in North Carolina and found that clinic directors see a need for co-located RSH services; however, only approximately 50% provided HIV testing and contraceptives (2). Further, non-pregnant women receiving medication for opioid use disorder (MOUD) show high rates of RSH service utilization when such services are offered (6).

Relatively little data exist regarding overall RSH needs among patients with OUD, especially among men. One reason for this discrepancy may be the focus on the high unintended pregnancy rates experience by pregnant women with OUD. In a landmark treatment trial, MOUD participants had double the rate of unintended pregnancy (86%), compared to the general population (31–47%) (7). The high rates of unintended pregnancy among pregnant women with OUD may be traced back to limited contraceptive use (8) and barriers to accessing RSH services (9). For example, women with substance use disorders are 25% less likely than the general population to use contraceptives (8) and most frequently endorsed condom use (62%), while high efficacy contraceptive methods, such as intrauterine devices (8%), were less frequently endorsed. Condom use is even lower (approximately 20%) among men receiving MOUD (10, 11). This mismatch between the high unintended pregnancy rate and low use of high efficacy contraception could benefit from a broader understanding of the challenges faced by patients trying to achieve their RSH goals.

By broadening the understanding of RSH from a focus on pregnant women with OUD to one that includes women (non-pregnant and pregnant) and men with OUD we can better understand the extent RSH services are desired and what RSH services to co-locate. This study aims to: (1) describe interest in RSH services among people receiving MOUD; (2) characterize patient contraceptive method use, knowledge, acceptability, and barriers to use; and (3) determining if gender differences are present in RSH domains.

MATERIALS AND METHODS

This cross-sectional survey was conducted at a single clinic between September 2016 and April 2018. The Comprehensive Opioid Addiction Treatment (COAT) Clinic at West Virginia University serves patients with OUD receiving MOUD (at the time, exclusively buprenorphine/naloxone medication) and a mix of group and individual therapy sessions (12). All patients over the age of 18 were potential participants in this study. The West Virginia University Institution Review Board approved this study. Data were collected in accordance with the Declaration of Helsinki (2013).

Procedure

To collect this convenience sample, potential participants were approached in the therapy group meeting space after the group therapy session was completed. After providing a brief study description, those who were interested in the study stayed in the room and completed consent. After consent, each participant was provided a confidential ID to link surveys across study sessions. The linking document that contained participant IDs was also used to verify if the participant was already enrolled in the study. It is estimated that our recruitment efforts reached approximately 75% of the patients enrolled in the clinic during the study timeframe of whom over 50% participated in the study. The recruitment methodology, however, prevented careful evaluation of how many participants were approached or refused study participation.

Surveys were individually completed in the group setting using a 7" Amazon Fire capacitive touch screen tablets and REDCAP online survey software (13). Trained research staff spent time with each participant adjusting the font size and orienting them to the touch-screen device. Participants were provided a rubber-tipped non-active stylus to interact with the tablet computer if needed (e.g., long fingernails). Participants received a $10 gift card to a national retailer following survey completion. Research staff remained in the room to answer questions and troubleshoot device issues.

Measures

A multidisciplinary team (psychology, social work, public health, addiction medicine, obstetrics, and gynecology) developed the survey. The survey was piloted with 50 women to test the technology, determine ease of use, and assess overall survey length and acceptability. The final survey version took 15 min to complete and had a Flesch-Kincaid score equivalent to a sixth grade reading level. Colloquial terms (e.g., rubbers) and brand names (e.g., Trojan) were used, when possible, to enhance comprehension and compliment the medical terminology included in the survey. All questions were asked of both women and men with gender-specific tailoring when relevant. Any question could be skipped as deemed necessary by the participant. See supplement for the full questionnaire.

Reproductive Health

Survey questions related to RSH included past year sexual activity, sexual partner's gender, frequency of emergency contraception ("Plan B"), and whether they would ever consider ending a pregnancy early. Gender was assessed *via* self-report. Pregnancy intention was assessed with the One Key Question format. The One Key Question (OKQ) "would you like to get pregnant in the next year?" was developed as a concise way to determine pregnancy interest and provide a gateway to a more comprehensive discussion about reproductive health behaviors in primary care settings (14). Responses included yes, no, maybe, do not know. For men, the OKQ was adapted to "do you want to father a child in the next year?" Participants were asked about their interest in co-located RSH services in general and in terms of specific programming using a six-point Likert-scale from "definitely would" to "definitely would not."

Contraception

All participants were asked about their current contraceptive methods including both colloquial and brand name descriptions from a list of 12 common methods. Multiple responses were permitted. For analysis, contraceptive methods were separated into high, medium, and low efficacy tiers based on CDC criteria (15). Non-pregnant women reporting using high efficacy long-acting reversible contraceptives (LARCs) were asked about method use reasons and satisfaction. Satisfaction was rated with a five-point Likert-scale ranging from very satisfied to very dissatisfied. The same list of contraceptive methods was presented to determine contraceptive knowledge by method learned from a health professional. Participants reporting barriers to accessing contraceptives were asked to identify what barriers they faced from a list including (check all that apply): transportation, cost, time, availability, no local doctor, religious reasons, not a priority, and other (specify). Contraceptive decision-making agency captured who is responsible for contraceptive decisions, and contraceptive decision-making flexibility focused on whether contraceptive choices change based on the partner.

Data Analysis Strategy

Variables were assessed for missingness and outliers (z scores >3.29) (16) and results presented with group means and stratified by gender and pregnancy status when relevant. A Chi-square analysis was used to test proportion of individuals who endorsed emergency contraceptive use, interest in ending a pregnancy early, pregnancy intention (OKQ, "Do you want to get pregnant in the next year?"), interest in RSH services, current contraceptive use (any), contraceptive method awareness, and if they have ever experienced barriers to accessing contraception by differences among gender and pregnancy status. A series of one-way analysis of variance (ANOVA) was run for contraceptive method awareness separated by efficacy by gender and pregnancy status. A Fisher's Least Significant Difference *post hoc* test was used to determine significant differences by gender, pregnancy status and relevant variables. All analyses were conducted using SPSS v.25 (SPSS, Inc., Chicago, IL, United States) and criterion to reject the null hypothesis was set a $P < 0.05$.

RESULTS

Participant Demographics

Adults ($N = 225$; 163 women, 62 men) provided informed consent. Complete data was available from 212 and was included in data analyses. The average participant was 33 years old (SD = 8.2), White (92.9%), with 12.5 years of education (SD = 1.8), and had Medicaid (92.0%). Twenty-nine women were currently pregnant, and one man's partner was currently pregnant. Fourteen women had a hysterectomy, and 15 women were post-menopausal before the study began. See **Table 1** for full demographics separated by gender and pregnancy status.

Reproductive Health

Most participants were sexually active in the past year (88.7%). Few participants (3.3%) reported same sex partners. Overall, 27.8% of participants (27.8% of non-pregnant women, 41.4% of pregnant women, and 21.1% of men's partners) had ever used emergency contraception. Among the women, 65.7% of non-pregnant women ($n = 35$) and 33.3% of pregnant women ($n = 12$) reported using emergency contraception more than 2 times. There were no significant differences in ever using emergency contraception between non-pregnant women, pregnant women, and men [$\chi^2(2) = 3.95$, $P = 0.138$].

TABLE 1 | Participant characteristics.

	Non-pregnant women ($n = 126$)	Pregnant women ($n = 29$)	Men ($n = 57$)	Total sample ($n = 212$)
Variable		***M* (SD)**		
Age (years)	33.5 (8.2)	27.7 (6.0)	34.7 (8.2)	33.0 (8.2)
Education (years)	12.5 (1.8)	12.2 (1.3)	12.5 (2.1)	12.5 (1.8)
		***n* (%)**		
Race				
Non-White	12 (9.5)	1 (3.4)	2 (3.5)	15 (7.1)
White	114 (90.5)	28 (96.6)	55 (96.5)	197 (92.9)
Ethnicity				
Non-Hispanic/Latino	125 (99.2)	29 (100.0)	57 (100.0)	211 (99.5)
Hispanic/Latino	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.5)
Relationship				
Never married	41 (32.5)	3 (10.3)	20 (35.1)	64 (30.2)
Married	23 (18.3)	6 (20.7)	15 (26.3)	44 (20.8)
Divorced	19 (15.1)	3 (10.3)	6 (10.5)	28 (13.2)
Separated	8 (6.3)	5 (17.2)	3 (5.3)	16 (7.5)
Living with a partner	27 (21.4)	11 (37.9)	13 (22.8)	51 (24.1)
Widowed	8 (6.3)	1 (3.4)	–	9 (4.2)
Treatment group				
Weekly	69 (54.8)	25 (86.2)	37 (64.9)	131 (61.8)
Bi-weekly	27 (21.4)	4 (13.8)	12 (21.1)	43 (20.3)
Monthly	30 (23.8)	–	8 (14.0)	38 (17.9)
Previous child (yes)	111 (88.1)	20 (69.0)	34 (59.6)	165 (77.8)
Tobacco use (yes)	110 (87.3)	25 (86.2)	49 (86.0)	184 (86.8)
Medicaid (yes)	120 (95.2)	27 (93.1)	48 (84.2)	195 (92.0)

Endorsement for considering ending a pregnancy was low. Overall, 13.2% of participants (14.3% of non-pregnant women, 13.8% of pregnant women, and 10.5% of men) reported agreement with considering ending a pregnancy. There were no significant differences in agreeing with the statement, "I would consider ending/having my partner end a pregnancy early" between non-pregnant women, pregnant women, and men [$\chi^2(4) = 5.08$, $P = 0.279$].

Reproductive and Sexual Health Services in a Clinic

Reproductive and sexual health service interest is detailed in **Table 2**. Overall, 45.8% of participants (49.2% of non-pregnant women, 44.8% of pregnant women, and 38.6% of men) were interested in having general RSH services co-located at their clinic. There were no significant differences observed between gender and pregnancy status and interest in RSH services at their clinic [$\chi^2(8) = 9.18$, $P = 0.327$].

Many participants (44.8%) were interested in the hypothetical clinic based RSH services offering regular physical exams, 41.0% were interested in STD/STI testing, and 38.2% were interested in contraception education and administration. Gender-specific RSH service questions were asked. Women were interested in having pregnancy testing offered (27.0% of non-pregnant women and 34.5% of pregnant women). Men reported interest in services to help with erectile function (24.6%) and premature ejaculation (17.5%).

TABLE 2 | Interest in RSH services at MOUD clinic.

	Non-pregnant women ($n = 126$)	Pregnant women ($n = 29$)	Men ($n = 57$)	Total sample ($n = 212$)
Variable		***n* (%)**		
Interest in RSH services				
Definitely would	32 (25.4)	6 (20.7)	9 (15.8)	48 (22.6)
Probably would	30 (23.8)	7 (24.1)	13 (22.8)	50 (23.6)
Neutral	27 (21.4)	8 (27.6)	22 (38.6)	57 (26.9)
Probably would not	27 (21.4)	5 (17.2)	12 (21.1)	44 (20.8)
Definitely would not	10 (7.9)	3 (10.3)	1 (1.8)	14 (6.6)
RSH services of interest				
Contraceptive education and administration	48 (38.1)	17 (58.6)	16 (28.1)	81 (38.2)
STI/STD Testing	52 (41.3)	9 (31.0)	26 (45.6)	87 (41.0)
Regular physical exams	63 (50.0)	9 (31.0)	23 (40.4)	95 (44.8)
Pregnancy testing*	34 (27.0)	10 (34.5)	–	–
Ending a pregnancy*	9 (7.1)	2 (6.9)	–	–
Erectile function+	–	–	14 (24.6)	–
Premature ejaculation treatment+	–	–	10 (17.5)	–

RSH, reproductive and sexual health.
Reproductive health addresses the reproductive processes, functions, and system at all stages of life (e.g., contraceptive counseling); sexual health is a state of physical, mental, and social well-being in relation to sexuality (e.g., sexual functioning).
**Men were not asked questions about women specific services.*
+Women were not asked about male specific services.

Contraceptives

Contraceptive methods are detailed in **Table 3**.

Current Contraceptive Method

Current use of contraception was low for non-pregnant women (30.9%) and men (17.9%). For non-pregnant women, the most common form of contraceptive method was female/male sterilization (18.6%) followed by the implant (7.2%), intrauterine device (7.2%), and oral contraceptive (7.2%). Four non-pregnant women reported using condoms as a contraceptive. The most common form of contraceptive methods reported by men was the condom (12.5%) followed by partner tubal ligation (8.9%).

Among participants who were not currently pregnant, had not had a hysterectomy, or were not post-menopausal, most non-pregnant women (69.1%) and men (82.0%) were not currently using contraception. Among this sub-sample of participants not currently using contraception, 76.1% of non-pregnant women and 91.3% of men were not interested in using contraception. That is, among reproductive-aged non-pregnant women and men in this sample, 76.1% of non-pregnant women ($n = 51$) and 91.3% of men ($n = 42$) were not interested in having a pregnancy over the next year, not currently using contraception, and not interested in using contraception.

Reason for and Satisfaction With Using High Efficacy Long-Acting Reversible Contraceptives

Among the nine non-pregnant women who reported using the implant, most non-pregnant women choose the implant for being reliable in preventing pregnancy (77.8%), ease of use (55.6%), based on a healthcare provider's recommendation (55.6%), and for personal comfort (44.4%). Satisfaction for non-pregnant women who used the implant was high, with no non-pregnant women reporting any dissatisfaction, and the majority (66.7%) reported being very satisfied.

Among the eight non-pregnant women who reported using an IUD, most non-pregnant women chose an IUD for ease of use (87.5%), for being reliable in preventing pregnancy (87.5%), and for personal comfort (62.5%). Satisfaction for non-pregnant women who used an IUD was high, with no non-pregnant women reporting any dissatisfaction, and the majority (75.0%) reported being very satisfied.

Contraceptive Method Awareness

Contraceptive method awareness among 12 contraceptive methods is detailed in **Table 3**. Overall, the average participant was aware of 45.8% of contraceptive methods. Significant differences between non-pregnant women, pregnant women, and men by contraceptive method awareness were observed for total contraceptive method awareness ($F_{(2,209)} = 3.59$, $P = 0.029$). Non-pregnant women were aware of significantly more total contraceptive methods ($M = 5.9$; SD $= 3.7$) compared to men ($M = 4.3$; SD $= 4.1$). No significant differences were observed between the other groups and total contraceptive method awareness.

TABLE 3 | Contraceptive method awareness from a health professional.

	Non-pregnant women ($n = 126$)	Pregnant women ($n = 29$)	Men ($n = 57$)	Total sample ($n = 212$)		
Variable		***n* (%)**				
Awareness of high efficacy methods						
Implant	54 (42.9)	13 (44.8)	16 (28.1)	83 (39.2)		
Intrauterine device	68 (54.0)	14 (48.3)	17 (29.8)	99 (46.7)		
Female/male sterilization	64 (50.8)	14 (48.3)	21 (36.8)	99 (46.7)		
Awareness of medium efficacy methods						
Oral contraceptive	101 (80.2)	22 (75.9)	27 (47.4)	150 (70.8)		
Ring	59 (46.8)	14 (48.3)	18 (31.6)	91 (42.9)		
Diaphragm	50 (39.7)	7 (24.1)	19 (33.3)	76 (35.8)		
Patch	66 (52.4)	15 (51.7)	13 (22.8)	94 (44.3)		
Injectable	78 (61.9)	20 (69.0)	18 (31.6)	116 (54.7)		
Awareness of low efficacy methods						
Condoms	90 (71.4)	19 (65.5)	40 (70.2)	149 (70.3)		
Withdrawal	35 (27.8)	9 (31.0)	17 (29.8)	61 (28.8)		
Fertility awareness	19 (15.1)	4 (13.8)	7 (12.3)	30 (14.2)		
Abstinence	70 (55.6)	21 (72.4)	37 (64.9)	128 (60.4)		
None	7 (5.6)	2 (6.9)	8 (14.0)	17 (8.0)		
		***M* (SD)**			***F***	***P***
Total contraceptive method awareness	4.4 (4.0)	6.0 (3.8)	5.9 (3.7)	5.5 (3.9)	3.59	0.029
High efficacy methods	0.9 (1.2)	1.5 (1.2)	1.4 (1.3)	1.3 (1.2)	3.90	0.022
Medium efficacy methods	1.7 (2.0)	2.8 (1.8)	2.7 (1.7)	2.5 (1.9)	7.88	0.001
Low efficacy methods	1.8 (1.2)	1.7 (1.3)	1.8 (1.2)	1.7 (1.3)	0.15	0.859

Specifiers in the survey included: condoms (e.g., Trojans, rubbers, jimmies); injectable (depo injection; Provera); implant (Implanon, Nexplanon); intrauterine device (IUD); ring (NuvaRing); patch (Ortho Evra); oral contraceptive (the Pill); female/male sterilization (tubes tied; tubal ligation); fertility awareness (the rhythm method; menstrual cycle timing); Nexplanon was added as a descriptor for "implant" based on pilot testing.

Significant differences were observed for high efficacy contraceptive method awareness ($F_{(2,209)} = 3.90$, $P = 0.022$). Non-pregnant women were aware of more high efficacy contraceptive methods ($M = 1.5$; SD = 1.2) compared to men ($M = 0.9$; SD = 1.2). No significant differences were observed between the other groups and high efficacy contraceptive method awareness.

Significant differences were observed for medium efficacy contraceptive method awareness ($F_{(2,209)} = 7.88$, $P = 0.001$). Non-pregnant women were aware of more medium efficacy contraceptive methods ($M = 2.8$; SD = 1.8) compared to men ($M = 1.7$; SD = 2.0). Pregnant women were aware of more medium efficacy contraceptive methods ($M = 2.7$; SD = 1.7) compared to men ($M = 1.7$; SD = 2.0). No significant differences were observed between the other groups and medium efficacy contraceptive method awareness.

No significant differences were observed between non-pregnant women, pregnant women, and men and low efficacy contraceptive method awareness ($F_{(2,209)} = 0.15$, $P = 0.859$).

Barriers to Accessing Contraception

Among the non-pregnant women who reported barriers to accessing contraception (13.5%), the most likely barriers selected were transportation (88.2%), cost (52.9%), availability (52.9%), and time (47.1%). Among the pregnant women (31.0%) and men (10.5%) who reported barriers to accessing contraception, no theme emerged regarding specific barriers to accessing contraception from the list provided. However, pregnant women (31.0%) were roughly three times more likely than non-pregnant women (13.5%) and men (10.5%) to have experienced a barrier to accessing contraception [$\chi^2(2) = 6.93$, $P = 0.031$].

Contraceptive Decision-Making Agency and Flexibility

Contraceptive decision-making agency and flexibility is detailed in **Figure 1**. Contraceptive decision-making agency was significantly different between non-pregnant women, pregnant women, and men [$\chi^2(4) = 32.7$, $P < 0.001$]. Non-pregnant women (55.6%) and pregnant women (48.3%) were more likely to respond that contraceptive use was "my decision" compared to men (15.8%). Men were significantly more likely to respond that contraceptive use was "my partner's decision" (12.3%) and "both our decision" (71.9%) than non-pregnant women and pregnant women.

Contraceptive use flexibility was significantly different between non-pregnant women, pregnant women, and men [$\chi^2(4) = 27.4$, $P < 0.001$]. Non-pregnant women (69.0%) and pregnant women (62.1%) were more likely to respond that

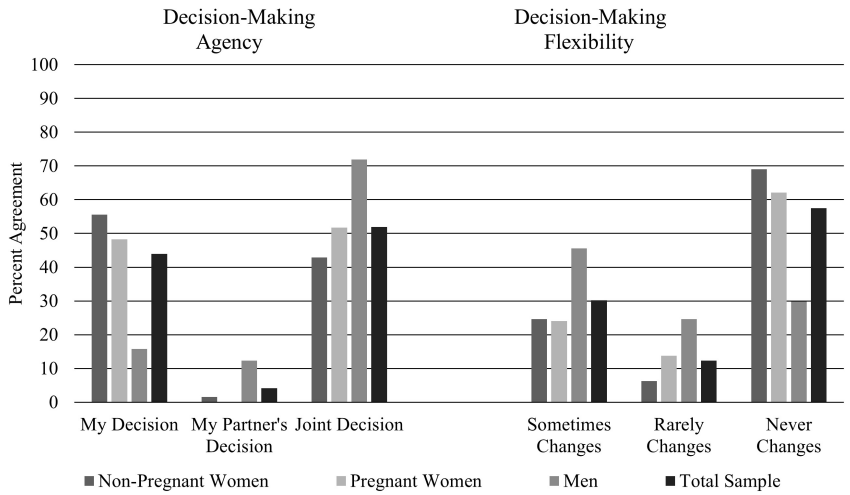

FIGURE 1 | Contraceptive decision-making agency and flexibility. Significant differences were observed between women and pregnant women and men for both decision-making agency and decision-making flexibility. Contraceptive decision-making agency was assessed with the question: "Whose decision is it to use birth control?" Contraceptive decision-making flexibility was assessed immediately after the contraceptive decision-making agency with the question: "Does the decision change depending on who the partner is?"

contraceptive use never changes depending on whom the partner is compared to men (29.8%). Men were significantly more likely to respond that contraceptive use was rarely (24.6%) and sometimes (45.6%) flexible depending on who the partner is.

DISCUSSION

To our knowledge, this is among the first empirical reports to document a range of RSH behaviors for both women *and* men with OUD receiving MOUD. By including women and men, we were able to understand some unique interests for each population. Overall interest in co-located RSH was high among both women and men. This contrasts with previous research that found limited co-located RSH services in OUD treatment facilities (2), suggesting a desired and unmet patient need.

Interest in Co-located Reproductive and Sexual Health Service

This work extends Black and associates (5) previous findings that 24.5% of women indicated a preference for women's health services to be integrated with MOUD. In the present study, approximately 40% of women and men were interested in same-day, co-located RSH services including contraception. Notably, the Black and associates study provided various settings that could accommodate RSH services (e.g., general practitioners and sexual health clinics) and was not assessing specific level of interest in co-located services at a MOUD treatment facility. In contrast, the present study was specific to co-located RSH services at a MOUD treatment facility.

Importantly, there may be a greater need for and interest in integrated services in rural populations. For example, the present study had a mean travel time of over 1 h, and most patients attend treatment for over 3 h per week. Interest in co-located services may be a necessity more than a matter of convenience for this sample. Additionally, the most common barriers faced when trying to access contraception were transportation, cost, and time. Co-located RSH services are one way to address these barriers. Nationally, the degree to which RSH services have been integrated into OUD treatment facilities is low; however, robust national data are lacking (2).

While the RSH service umbrella is large, our findings highlight often overlooked elements of comprehensive care. For example, both women and men were interested in STI/STD testing at a co-located RSH clinic. There was also interest in male specific services such those that focus on premature ejaculation treatments and erectile function. This aligns with potential sexual dysfunction associated with opioid use (17–20); however, treatment for these related conditions are often overlooked as part of comprehensive care or focused RSH services. While emergency contraception was not included as a potential "service" to be offered at clinics in our survey, between 27 and 41% of women reported its use suggesting that questions about emergency contraception should be included in future research. Additionally, consideration of ending a pregnancy early was 13.2% across the complete sample suggesting that ethical counseling related to ending a pregnancy grounded in respect for patient autonomy should also be the standard of care at OUD clinics that integrate RSH services.

Contraceptive Knowledge and Use

Participants in this sample were also interested in contraceptives being included in co-located RSH services. Although interest in co-located contraceptive counseling was high, current contraceptive use and knowledge about contraception was low, in both men and women. Knowledge of high and medium efficacy approaches was low overall but lower among men than women. Both groups knew similar amounts of low efficacy approaches.

The lack of knowledge regarding high efficacy LARCs may contribute to both the high rates of unintended pregnancy and ambivalence around contraceptive use. Women who used high-efficacy LARCs (e.g., IUD) reported more satisfaction with their use, few women had previous knowledge about high-efficacy LARCs which may explain why only 46% of participants were interested in contraceptive services at the clinic and be a target of future interventions.

Among the non-pregnant sub-sample, most women and men were not interested in having a pregnancy over the next year; however, they were not currently using contraception, and were not interested in using contraceptives. This counterintuitive finding can be understood in several ways. First, while counterintuitive that individuals who do not want a pregnancy in the next year are also not engaging in contraceptive use, low knowledge of high efficacy contraceptives may be one explanation borne out in our findings. Second, it is worth noting that our sample is on the low end of condom use (4.3% of women and 12.5% of men) compared to the Terplan and associates (8) review of women with substance use disorders (range of 3–87%) and the approximately 9% of reproductive-age women in the United States who reported male condom use between 2015 and 2017 (21). While low, condom use in our sample may be accurate, it is also possible that because the question assessed "birth control" use, there may have been some underreporting due to confusion. It is possible that condoms are not always thought of as a form of "birth control" and are more associated with HIV and STI/STD prevention, especially in OUD patient populations where contraceptive materials are often tailored toward the dual role of HIV prevention and contraception. Third, low interest in contraceptive approaches may be due to low knowledge of high efficacy approaches from health professionals that require less daily maintenance and are relatively new (e.g., implants and IUDs) compared to approaches that need constant attention and are more commonly used in the United States (e.g., the Pill and condoms). Indeed, among participants in our sample who reported use of high efficacy LARCs, satisfaction was high. They were preferred for their ease of use (55.6–87.5%), reliably preventing pregnancies (77.8–87.5%), and personal comfort (44.4–62.5%) for implants and IUDs, respectively. While LARC use was low in this sample, this indicates that these methods can be acceptable to women with OUD, and knowledge may be a barrier to more widespread use.

Previous research has shown that high-efficacy contraceptive use is low among patients with an OUD (8). While evidence-based contraception counseling methods can help increase knowledge about newer contraceptives (22), education alone may not ultimately lead to new behaviors unless other barriers are addressed, such as access that can occur through co-located services. Contraceptive decision-making does not happen in a vacuum. Women were more likely to report contraceptive use as their decision and that this decision is not flexible. In contrast, men were more likely to report that it is a joint decision and that there is some flexibility in contraceptive use depending on the partner. These discordances between knowledge and decision-making by gender could make for challenging discussions between partners regarding contraceptive method choice. As such, educational initiatives aimed at contraception should be inclusive of men as they may play a role in contraceptive decision making and are less likely to be familiar with high efficacy approaches. Recent research shows that providing either face-to-face or computerized RSH services using a shared decision making approach, between provider and patient, to non-pregnant women receiving MOUD hold promise for increasing both decision making and follow through on a contraceptive practice decision compared to usual care (6). Increasing access to person-centered contraceptive counseling through co-located RSH services can help better fulfill the health needs of this patient population and have been shown to be cost effective (23).

Limitations of the Current Study

This study is not without limitations. Our study was at a single site in which may limit generalizability of our findings to OUD patients receiving MOUD in different geographic locations with different access to RSH services. While sexual health applies to all participants in the study, reproductive health may not. Future research may consider separating out these domains. In this study, gender was only presented as a binary choice (male and female) and did not include the full spectrum of potential gender identities. This was a cross-section survey without follow-up; thus, causality could not be determined. Additionally, while the study included men and women, it was only piloted in women because there were relatively few men attending this clinic. Lastly, our sample was 92.9% white and primarily women. While this is representative of the clinic, this is not representative of OUD. Future work should address these limitations in more diverse samples. Despite this weakness, this study has unique strengths. It is the first to document interest in the co-located RSH services into addiction treatment in women and men and broadly characterize contraceptive knowledge and decision making.

CONCLUSION

Based on these findings, we recommend that both contraceptive counseling and provision of contraceptives be provided at MOUD programs due to the co-occurring low knowledge of contraceptive options and low utilization of high-efficacy, reversible methods. Most MOUD clinics have staff that could be trained to provide most LARC methods. If a patient receives their MOUD at their primary care providers office or a federally qualified health center, then these services are already available; however, most patients receive their care at a MOUD clinic, highlighting the need to co-locate RSH services in traditional treatment settings.

Co-located RSH and MOUD services are beneficial and a substantial minority of both women *and* men in our study are interested in various co-located RSH services. Co-located RSH and MOUD services are especially important in rural communities with limited access to these services. Knowledge of contraceptive methods and use of contraception was low. Contraceptive decisions varied based on interpersonal dynamics in our participants' relationships. These factors underscores the importance of assessing the RSH needs of both men and

women in OUD treatment. Taken together, providing RSH services may allow for increased RSH education, increased uptake of contraceptive methods, and healthier life outcomes. This research suggests that including RSH services would not only address an un-met need but would move addiction treatment to be more holistic.

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 West Virginia University Institution Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors were involved in the conceptualization and methodology of the work described in this manuscript, contributed substantively to the content of the manuscript, and review and editing of the manuscript. JS, LL, and JP handled the project management. JS led analyses and manuscript writing. All authors have approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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E-cigarettes and non-suicidal self-injury: Prevalence of risk behavior and variation by substance inhaled

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Background: Nicotine and cannabis inhalation through vaping or electronic delivery systems has surged among young adults in the United States, particularly during the coronavirus disease pandemic. Tobacco and marijuana use are associated with select adverse mental health outcomes, including symptoms of major depressive disorder and suicidal behaviors. Given the need for addiction specialists to treat problematic substance use with an integrated approach, the association between non-suicidal self-injury (NSSI) and use of e-cigarettes, tobacco, marijuana, and alcohol was examined among a diverse sample of college students.

Methods: Healthy Minds Study data from 47,016 weighted observations, collected from college students in the 2018–2019 academic year, was used to explore associations between NSSI-related behaviors and past 30-day use of a vaping product (nicotine or marijuana). These relationships were assessed among those using vaping products only, and then among individuals using vaping products and alcohol, conventional cigarettes, and/or marijuana. Hierarchical logistic regression models estimating the relationship between vaping and NSSI were computed to adjust for the effects of demographic factors, symptomatology of psychiatric disorders, and concurrent use of other substances.

Results: A fifth (22.9%) of respondents disclosed past 12-month NSSI; they were significantly more likely to screen positive for depression or anxiety compared to young adults without NSSI. Rates of using vaping products, conventional cigarettes, marijuana, or other substances were higher among students with NSSI even after controlling for potential cofounders. Additionally, students who used a THC-based liquid in their e-cigarettes were more likely to endorse NSSI in comparison to those who used "just flavoring." However, young adults who vaped were less likely to disclose frequent NSSI-related behaviors than their peers who did not vape.

Conclusions: These findings revealed an association between past 12-month NSSI and past 30-day vaping in a sample of young adults. Further surveillance among college populations and examination of potential sociodemographic confounders is necessary to confirm these findings and advance the substance use and addiction field.

KEYWORDS

non-suicidal and suicidal self-injurious thoughts and behaviors, e-cigarette, marijuana, conventional cigarette, substance use (drugs, vaping, alcohol)

Introduction

Over the past 6 years, young adult use of e-cigarette and vaping products has increased to epidemic-level proportions (1–3). In part, this may be the consequence of vaping misinformation delivered via social media platforms and by peers who use e-cigarettes, outlets regarded by college-aged adults as credible sources of information about vaping products (4). In addition to positive social media messages promoting the use of e-cigarettes and other vaping products (5), multinational tobacco companies' marketing initiatives endorse e-cigarettes as a less harmful alternative to cigarette smoking (1, 6). However, research indicates both short- and long-term health risks associated with youth vaping (1, 2, 7–9), posing a particularly problematic public health concern.

E-cigarette use is associated with other risky health behaviors (e.g., binge drinking and use of other substances) and negative health outcomes (1, 2, 7, 9–17). Symptoms of mental health problems are also common among young people who use e-cigarettes. For instance, young adult use of vaping products has been associated with depression, disordered eating, ADHD, conduct disorder, anxiety, and PTSD (14, 18). Vaping nicotine alone or marijuana use alone or dual-use have all been associated with depressive symptoms and suicidal behaviors (19). Furthermore, a relationship has been observed between using e-cigarettes and suicidal ideation and attempts among youths. The use of e-cigarettes was associated with a 23% increased odds of seriously considering attempting suicide in the prior year among more than 25,000 adolescents participating in the US Youth Risk Behavior Survey (YRBS) (3). Dual-use increased the odds of suicidal behaviors even more in the same survey (3). Additionally, a medically serious suicide attempt was endorsed by one in 20 (5.6%) respondents endorsing e-cigarette use compared to fewer than one in 150 individuals who did not disclose e-cigarette use (0.6%) in a nationwide sample of Korean adolescents (20).

Non-suicidal self-injury (NSSI), defined as intentional and self-directed behavior(s) leading to physical harm without suicidal intent nor expectation of mortality (21–24), may also be linked to e-cigarette use/vaping. Approximately one in five (19.8%) college students in the United States (US) endorse past-12 month NSSI (25); pooled lifetime prevalence among adults between 18 and 24 years is slightly lower (13.4%) (26). While NSSI is highly heterogeneous in type, frequency, and severity (27), the behavior has been identified as a strong predictor of poor mental health outcomes, including stress, anxiety, and emotional dysregulation (28, 29). NSSI during adolescence increases the risk of attempting suicide during adulthood (30). Prior work has examined whether changes in the number of Google searches related to suicide is associated with changes in suicide rates (31). Importantly, NSSI during adolescence remains a significant risk factor for negative mental health in young adulthood, regardless of the frequency or stability of the behavior (29).

Despite emerging research reporting a positive association between vaping and marijuana use and suicidal behaviors, and specifically between vaping and suicide attempts, the relationship between substance use, NSSI, and suicidal behaviors remains understudied. This investigation aims to evaluate the relationship between the use of e-cigarettes, marijuana use, smoking, and alcohol use, and NSSI behavior using data collected from undergraduate and graduate students participating in the 2018–2019 Health Minds Study (HMS), an annual, internet-based survey assessing the mental health status and health care utilization of college students in North America. We hypothesized that students using e-cigarettes would be more likely to report NSSI behavior than those reporting no use and that the strength of this relationship would increase as the frequency of NSSI behavior increased. We further hypothesized that the strength of the relationship between e-cigarette use and NSSI would vary by the type of substance inhaled. Specifically, we postulated that students inhaling nicotine and marijuana-based e-liquids would be more likely to report NSSI, compared to those inhaling flavoring only. This study may assist clinicians in enhancing screening instruments to identify college populations at a greater risk for adverse mental health outcomes.

Materials and methods

This secondary data analysis includes data collected from 35,777 undergraduate and graduate students participating in the HMS between Fall 2018 and Spring 2019. Since 2007, the HMS

team has collected information from more than 400,000 students attending 350 colleges and universities primarily located in the United States. Participant recruitment and data collection methods have been described elsewhere (32, 33).

In short, random samples of 4,000–20,000 degree-seeking students at large, participating institutions (or all students at smaller institutions), 18 years of age and older, were recruited to participate via email invitations. Invitations provided a personalized link to a web page with more information on the study and an informed consent page. The page indicated the study purpose was to examine mental health and related issues as well as service utilization among college students. Between 2018 and 2019, approximately 16% of students who were invited to participate completed the web-based survey. To reduce non-response bias, the HMS team has constructed non-response weights using administrative data on full student populations (variables include gender, race/ethnicity, academic level, and grade point average). Accordingly, this data analysis includes 47,016 weighted observations (35,777 observations) that provided information related to substance use behavior, non-suicidal self-harm, and mental health symptomatology.

Demographics

Students were asked to provide their age (coded as 18–25, 25+), gender (coded as male, female, trans male/trans man, trans female/transwoman, genderqueer/gender non-conforming, self-identify; recoded as male, female), and race (coded as African American/Black, American Indian or Alaskan Native, Asian American/Asian, Hispanic/Latino/a, Native Hawaiian or Pacific Islander, Middle Eastern/Arab/Arab American, White, Other; recoded as white, non-white). While the information from students who did not identify as male or female would be extremely valuable to the field, due to the small sample size in the Healthy Minds sample (trans male/trans man: $N = 173$, trans female/transwoman: $N = 81$, genderqueer/gender non-conforming: $N = 500$, self-identify: $N = 382$), only those who identified as male or female were included in this analysis.

Non-suicidal self-injurious behaviors (NSSI)

Students were provided a list of non-suicidal self-injurious behaviors and were asked to consider ways they may have hurt themselves on purpose, without intending to kill themselves. Past 12-month history of the following behaviors was assessed: (1) cutting oneself, (2) burning oneself, (3) punching or banging oneself, (4) scratching oneself, (5) biting oneself, (6) pulling one's hair, (7) punching or banging an object, (8) interference with wound healing, (9) carving words or symbols into the skin, and (10) rubbing sharp objects into the skin. Participants were provided a comment field to specify other self-injurious behaviors as appropriate. Students who reported past 12-month NSSI were asked about the frequency of self-injurious behavior over the last year (once or twice, once a month or less, 2 or 3 times a month, once or twice a week, 3 to 5 days a week, nearly everyday or everyday). A two-category variable was created to denote frequent NSSI behavior (i.e., behavior occurring 2 or 3 times a month or more) or no frequent NSSI behavior (behavior occurring less than that).

E-cigarette use

Students were asked about their past 30-day use of e-cigarettes and vaping products. Respondents who endorsed past 30-day use were classified as students who currently use an e-cigarette. These individuals were further queried about the type of mist inhaled at last use and were asked to select one of the following: nicotine, marijuana (hereafter referred to as THC for Delta-9-tetrahydrocannabinol), "just flavoring," or any vaping. Those who did not endorse past 30-day use were classified as not currently using e-cigarettes.

Use of other substances

To assess the use of conventional cigarettes, participants were asked to report the number of cigarettes smoked per day over the last 30 days. Students smoking one or more cigarettes per day were classified as currently using conventional cigarettes and those who reported smoking zero cigarettes were classified as individuals who did not use conventional cigarettes. Students were also asked about past 30-day use of marijuana (yes/no) and past 30-day use of other substances (yes/no), including cocaine, heroin, methamphetamines, ecstasy, non-prescribed opioid pain relievers (such as Vicodin and OxyContin), non-prescribed stimulants (such as Ritalin and Adderall), and other drugs without a prescription. Finally, students were asked to report past 2-week alcohol use (yes/no).

Psychiatric symptomatology

Students completed the Patient Health Questionnaire (PHQ-9) (34, 35) and the Generalized Anxiety Disorder 7-item (GAD-7) scale (36) to assess the current symptomatology of depression and anxiety, respectively. Those with a PHQ-9 total score of 15 or greater were classified as having moderately severe or severe depression, and those with a GAD-7 total score $\geq$10 were classified as having moderate or severe anxiety. Scores below the cut points were classified as not having moderately severe depression or anxiety.

TABLE 1 Demographic overview of study sample, by past 12-month self-injury.

	Past-year NSSI $N = 10,757$ (%)	No past-year NSSI $N = 36,259$ (%)	p
Gender			<0.0001
Male	4,143 (38.5)	15,741 (43.4)	
Female	6,613 (61.5)	20,517 (56.6)	
Age			<0.0001
18–25 years	9,673 (89.9)	27,657 (76.3)	
26+ years	1,084 (10.1)	8,601 (23.7)	
Race			0.0084
White	7,027 (65.3)	22,793 (62.9)	
Non-white	3,730 (34.7)	13,466 (37.1)	
Depression symptoms			<0.0001
Moderate–Severe	4,198 (39.0)	4,164 (11.5)	
None–Mild	6,559 (61.0)	32,095 (88.5)	
Anxiety symptoms			<0.0001
Moderate–Severe	6,009 (55.9)	8,678 (23.9)	
None–Mild	4,748 (44.1)	27,581 (76.1)	

TABLE 2 Substance use behavior, by past 12-month self-injury.

	Past-year self-injury $N = 10,757$ (%)	No past-year self-injury $N = 36,259$ (%)	p
Electronic cigarette use	2,901 (27.0)	5,854 (16.1)	<0.0001
Conventional cigarette use	1,747 (16.2)	3,088 (8.5)	<0.0001
Marijuana use	4,048 (37.6)	7,156 (19.7)	<0.0001
Alcohol use	6,615 (61.5)	20,571 (56.7)	<0.0001
Use of other substances	966 (9.0)	1,428 (3.9)	<0.0001

TABLE 3 Substance use behavior, by past 12-month NSSI AND suicidal ideation ($N = 46,883$).

	NSSI + Ideation $N = 3,932$ (%)	NSSI Only $N = 6,794$ (%)	No NSSI $N = 36,157$ (%)	p
E-cig use	1,158 (29.4)	1,726 (25.4)	5,847 (16.2)	<0.0001
Conv. Cig use	742 (18.9)	1,001 (14.7)	3,070 (8.5)	<0.0001
Marj. use	1,648 (41.9)	2,389 (35.2)	7,142 (19.8)	<0.0001
Alc. use	2,455 (62.4)	4,137 (60.9)	20,515 (56.7)	<0.0001
Other Sub. use	426 (10.8)	540 (7.9)	1,425 (3.9)	<0.0001

Statistical analysis

Using Pearson's chi-squared tests, we compared the demographic characteristics, psychiatric symptomatology, and substance use behaviors of students endorsing past 12-month NSSI to that of students endorsing no self-injury (Tables 1, 2). Variation in substance use behavior was assessed among college students reporting NSSI and suicidal ideation, those reporting NSSI only (i.e., no suicidal ideation), and those reporting neither NSSI nor suicidal ideation (Table 3; Analysis limited to students who provided information regarding past-year suicidal intent [In the past year, did you ever seriously think about attempting suicide? (yes/no)], $N = 46,883$). Additionally, among those endorsing the use of e-cigarettes, we considered whether students endorsing both e-cigarette use and other substance use behavior were more likely to report NSSI than those using e-cigarettes alone (Table 4).

Three sets of hierarchical logistic regression models were then used to assess the relationship between the use of e-cigarettes and past 12-month NSSI (Table 5). In the first set of models, the unadjusted association between past 30-day use of e-cigarettes and NSSI was assessed, and three additional models successively added the effects of (1) demographic characteristics, (2) psychiatric symptomatology, and (3) use of other substances. In the second set of models, we assessed whether the type of e-liquid inhaled predicted the odds of past 12-month NSSI among those using e-cigarettes, again controlling for the effects of demographic characteristics, psychiatric symptoms, and substance use behavior. In the final set of models, the association between the use of e-cigarettes and NSSI frequency was assessed among those reporting any past 12-month self-injurious behavior, adjusting for the aforementioned covariates.

Results

One in five students ($N = 10,756.8$ [rounded to 10,757], 22.9%) endorsed past 12-month non-suicidal self-injury, of whom 21.3% ($N = 2,296$) reported NSSI behavior 2 or more times per month. Compared to those who reported no self-injurious behavior ($N = 36,258.5$ [rounded to 36,259]), students reporting past 12-month NSSI were more likely to be female (61.5% vs. 56.6%, $p < 0.0001$), White (65.3% vs. 62.9%, $p < 0.0001$), and between the ages of 18 and 25 (89.9% vs. 76.3%, $p < 0.0001$; Table 1). Those reporting NSSI were also more than twice as likely to report moderate or severe anxiety symptoms (55.9% vs. 23.9%, $p < 0.0001$) and over three times as likely to report moderately severe or severe symptoms of depression (39.0% vs. 11.5%, $p < 0.0001$) when compared to peers who did not endorse NSSI.

TABLE 4 Concurrent substance use behavior among individuals using e-cigarettes (N = 8,755), by past 12-month NSSI.

	Past-year NSSI $N = 2,901$ (%)	No past-year NSSI $N = 5,854$ (%)	p
Conventional cigarette use			<0.0001
E-cig – Conv. Cig use	1,795 (61.9)	4,433 (75.7)	
E-cig + Conv. Cig use	1,106 (38.1)	1,421 (24.3)	
Marijuana use			<0.0001
E-cig – Marj. Use	903 (31.3)	2,760 (47.2)	
E-cig + Marj. Cig	1,998 (68.9)	3,094 (52.8)	
Alcohol use			0.7242
E-cig – Alc. use	539 (18.6)	1,058 (18.1)	
E-cig + Alc. Use	2,361 (81.4)	4,796 (81.9)	
Use of other substances			<0.0001
E-cig – Other Sub.	2,280 (78.6)	5,078 (86.8)	
E-cig + Other Sub.	621 (21.4)	775 (13.2)	
Number of substances used			<0.0001
E-cig use only	198 (6.8)	613 (10.5)	
E-cig + 1–2 substances	1,746 (60.2)	4,131 (70.6)	
E-Cig + 3–4 substances	926 (31.9)	1,081 (18.5)	
E-Cig + 5+ substances	31 (1.1)	29 (0.5)	

Substance use

In comparison to those who reported no self-injurious behavior, participants reporting NSSI more frequently endorsed the use of all substances, including electronic cigarettes (Table 2). In particular, more than one in four students reporting NSSI behavior also reported the use of e-cigarettes, compared to one in six students who did not report NSSI. Further, those endorsing past 12-month NSSI were approximately twice as likely to report the use of conventional cigarettes (16.2% vs. 8.5%, $p < 0.0001$) and marijuana (37.6 vs. 19.7%, $p < 0.0001$), and nearly three times as likely to report the use of other substances (9.0% vs. 3.9%, $p < 0.0001$). Students endorsing NSSI were also slightly more likely to report past 2-week alcohol consumption (61.5% vs. 56.7%, $p < 0.0001$) compared to those reporting no self-injurious behavior.

When compared to students who endorsed NSSI only (no suicidal ideation) and those with neither NSSI nor suicidal ideation, participants who reported both past 12-month NSSI and suicidal ideation were more likely to report use of e-cigarettes (NSSI + suicidal ideation: 29.4%; NSSI only: 25.4%; no NSSI: 16.2%; $p < 0.0001$), conventional cigarettes (NSSI + suicidal ideation: 18.9%; NSSI only: 14.7%; no NSSI: 8.5%; $p < 0.0001$), marijuana (NSSI + suicidal ideation: 41.9%; NSSI only: 35.2%; no NSSI: 19.8%; $p < 0.0001$), alcohol (NSSI + suicidal ideation: 62.4%; NSSI only: 60.9%; no NSSI: 56.7%; $p < 0.0001$), and other substances (NSSI + suicidal ideation: 10.8%; NSSI only: 7.9%; no NSSI: 3.6%; $p < 0.0001$) (Table 3).

Multiple substance use

To further understand the relationship between substance use behaviors, including vaping, and NSSI, we assessed variation in current substance use behavior by NSSI among those who endorsed vaping ($N = 8,755$). Specifically, we assessed the relationships between the use of conventional cigarettes only, marijuana only, alcohol only, and other substance (none, 1–2, 3–4, 5+) and NSSI among students reporting the use of e-cigarettes. In comparison to those who reported no self-injurious behavior, participants who endorsed NSSI were significantly more likely to report the use of both e-cigarettes and conventional cigarettes (38.1% vs. 24.3%, $p < 0.0001$), as well as the use of both e-cigarettes and marijuana (68.9% vs. 52.8%, $p < 0.0001$). However, those reporting NSSI were no more likely to report the use of both e-cigarettes and alcohol than those who reported no NSSI behavior. When the number of additional substances used was summed, those endorsing NSSI were almost twice as likely as those without NSSI to report the use of e-cigarettes and 3–4 or 5+ other substances (31.9% vs. 18.5% and 1.1% vs. 0.5% respectively, both $p < 0.0001$; Table 4).

Hierarchical logistic regression models

The results of all hierarchical logistic regression models are displayed in Table 5. In our first set of hierarchical logistic regression models assessing the association between past 30-day use of e-cigarettes and NSSI, we found that past 30-day e-cigarette use increased the odds of NSSI 2-fold (OR: 1.92, 95% CI: [1.76, 2.10], $p < 0.0001$). The size of the effect was reduced incrementally with adjustment for (1) demographic characteristics (aOR: 1.77, 95% CI: [1.61, 1.93], $p < 0.0001$), (2) psychiatric symptomatology (aOR: 1.54, 95% CI: [1.40, 1.70], $p < 0.0001$), and (3) co-occurring substance use behavior (aOR: 1.27, 95% CI: [1.14, 1.40], $p < 0.0001$). However, the relationship between e-cigarette use and NSSI remained significant in all models.

In our second set of hierarchical logistic regression models assessing the relationship between the type of e-liquid inhaled and NSSI among individuals using e-cigarette(s), we found that individuals vaping THC-based e-liquids were 66% more likely to report past 12-month NSSI than students vaping "just flavoring" after controlling for relevant covariates (aOR: 1.66, 95% CI: [1.11, 2.47], $p = 0.0127$). However, we observed no difference in NSSI behavior between students vaping nicotine-based e-liquids and those vaping "just flavoring" (aOR: 1.09, 95% CI: [0.77, 1.54], $p = 0.6359$).

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TABLE 5 Hierarchical logistic regression models.

E-cigarette use and past 12-month NSSI (weighted $N = 47,016$)

	Model 1 OR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)	Model 4 aOR (95% CI)
Exposure of interest				
Electronic cigarette use	1.92 (1.76, 2.10)	1.77 (1.61, 1.93)	1.54 (1.40, 1.70)	1.27 (1.14, 1.40)
Demographics				
Gender (Female)	–	1.29 (1.19, 1.40)	1.07 (0.98, 1.16)	1.09 (0.99, 1.18)
Age (18–25 years)	–	2.58 (2.29, 2.91)	2.49 (2.20, 2.82)	2.60 (2.30, 2.95)
Race (White)	–	1.02 (0.94, 1.11)	–	–
Psychiatric symptoms				
Moderate–Severe depression	–	–	2.76 (2.48, 3.06)	2.69 (2.42, 2.99)
Moderate–Severe anxiety	–	–	2.46 (2.24, 2.70)	2.45 (2.32, 2.69)
Substance use				
Conventional cigarette use	–	–	–	1.67 (1.46, 1.90)
Alcohol use	–	–	–	1.07 (0.98, 1.16)
Use of other substances*	–	–	–	1.49 (1.26, 1.75)
E-liquid inhaled and past 12-month NSSI (weighted $N = 8,358$)				
Exposure of interest				
THC E-Liquid (vs. "just flavoring")	1.69 (1.19 2.40)	1.81 (1.27, 2.58)	1.82 (1.23, 2.70)	1.66 (1.11, 2.47)
Nicotine E-Liquid (vs. "just flavoring")	1.23 (0.90, 1.68)	1.32 (0.96, 1.82)	1.36 (0.96, 1.93)	1.09 (0.77, 1.54)
Demographics				
Gender (Female)	–	1.38 (1.17, 1.64)	1.11 (0.92, 1.32)	–
Age (18–25 years)	–	2.34 (1.69, 3.24)	2.35 (1.63, 3.38)	2.53 (1.73, 3.70)
Race (White)	–	0.74 (0.62, 0.88)	0.83 (0.68, 1.00)	–
Psychiatric symptoms				
Moderate–Severe depression	–	–	2.80 (2.27, 3.45)	2.73 (2.21, 3.36)
Moderate–Severe anxiety	–	–	2.36 (1.94, 2.87)	2.42 (1.99, 2.94)
Substance use				
Conventional cigarette use	–	–	–	1.87 (1.53, 2.27)
Alcohol use	–	–	–	0.92 (0.73, 1.15)
Use of other substances*	–	–	–	1.41 (1.12, 1.78)
E-cigarette use and frequent NSSI (i.e., 2 or more times per month; weighted $N = 10,354$)				
Exposure of interest				
Electronic cigarette use	0.77 (0.63, 0.93)	0.76 (0.62, 0.92)	0.69 (0.57, 0.83)	0.73 (0.60, 0.90)
Demographics				
Gender (Female)	–	1.00 (0.83, 1.20)	–	–
Age (18–25 years)	–	1.25 (0.94, 1.70)	–	–
Race (White)	–	1.02 (0.85, 1.21)	–	–
Psychiatric symptoms				
Moderate–Severe depression	–	–	2.06 (1.68, 2.53)	2.05 (1.67, 2.52)
Moderate–Severe anxiety	–	–	1.52 (1.23, 1.88)	1.51 (1.22, 1.88)
Substance use				
Conventional cigarette use	–	–	–	0.95 (0.75, 1.22)
Alcohol use	–	–	–	0.77 (0.65, 0.92)
Use of other substances*	–	–	–	1.10 (0.81, 1.49)

* Not including marijuana.

In our final set of hierarchical logistic regression models evaluating the association between use of e-cigarettes and NSSI frequency among those reporting any past 12-month self-injurious behavior, students using electronic cigarettes were less likely to report frequent self-injurious behavior (i.e., 2 or more times per month) compared to those not using e-cigarettes (OR: 0.77, 95% CI: [0.63, 0.93], $p = 0.0058$). This relationship remained significant after controlling for (1) demographic characteristics (aOR: 0.76, 95% CI: [0.62, 0.92], $p = 0.0045$), (2) psychiatric symptomatology (aOR: 0.69, 95% CI: [0.57, 0.83], $p = 0.0001$), and (3) co-occurring substance use behavior (aOR: 0.73, 95% CI: [0.60, 0.90], $p = 0.0023$). Of note, conventional cigarette use and use of other substances were not significant predictors of NSSI frequency.

Types of NSSI behavior endorsed by students using e-cigarette(s)

Pearson's chi-squared tests were used to examine the types of NSSI behaviors most frequently endorsed by students using e-cigarettes and those not using e-cigarettes. For almost all behaviors assessed, those using e-cigarettes were nearly twice as likely to endorse NSSI compared to individuals not using e-cigarettes. Among both students using e-cigarettes and those not using e-cigarettes, the most frequently endorsed self-injurious behaviors included (1) punching or banging oneself (13.4% vs. 7.6%, $p < 0.0001$), (2) punching or banging an object to hurt oneself (12.6% vs. 6.0%, $p < 0.0001$), (3) scratching oneself (12.0% vs. 8.2%, $p < 0.0001$), (4) pulling one's own hair (11.0% vs. 6.8%, $p < 0.0001$), (5) interference with wound healing (10.6% vs. 6.1%, $p < 0.0001$), and (6) cutting oneself (10.1% vs. 4.6%, $p < 0.0001$).

Discussion

Using a large, national sample of college students, we examined associations between specific types of deliberate self-injurious behaviors and use of e-cigarettes, including specific types of liquid used in these devices, conventional cigarettes, and alcohol use. With almost 11,000 students endorsing deliberate self-injurious behavior in the prior year, we also had the power to comprehensively characterize the demographic and mental health profile of students who engage in NSSI and to evaluate the frequency of other substance use behaviors in this population. All variables were significantly different between those with past-year NSSI and with no endorsed NSSI, with younger, White women who endorsed moderate to severe symptoms of anxiety and depression more likely to report self-injurious behavior. When assessed individually, past-year NSSI was also more likely to be disclosed by those who also endorsed the use of e-cigarettes, conventional cigarettes, marijuana, alcohol, or other substances.

None of these results are surprising; rather they confirm what is already known among other samples. Prior literature indicates much higher rates of NSSI among youths using conventional cigarettes, THC, and other illicit substances (37). Indeed, in a systematic review of 36 studies investigating the relationship between substance use and self-injurious behavior in non-clinical samples, all but four studies found substance use to be significantly associated with self-injury (38). Some have postulated a link between substance use and NSSI through emotional (39) or affective (38) dysregulation, although the present study is not able to elucidate the mechanisms underlying the observed relationships. Nevertheless, the association between NSSI and e-cigarette use is concerning and suggests that addiction specialists should screen young adults using e-cigarette(s) for self-injurious behaviors. Combined with prior literature, our findings also support the need for integrative addiction medicine teams to ensure that patients, particularly college students, who would benefit from both mental health and substance use treatment, receive timely and adequate care.

We added to the literature by clarifying the relationship between e-cigarette use and other drug use and NSSI, and then by developing a set of hierarchical logistic regression models that display the continued importance of the association between vaping and past 12-month NSSI when controlling for all the other significant variables. Importantly, alcohol use did not add to the risk of NSSI while all other additional substances did, both independently and when added together. Indeed, using 3 or more substances in addition to e-cigarette use nearly doubled the risk of NSSI. Hierarchical models showed that risk for NSSI was heightened among younger, White women with affective symptoms, but that beyond these characteristics, engaging in vaping, smoking, and other substance use each contributed uniquely to predict NSSI.

Further, because of the increased recognition that young adults commonly vape liquid substances such as THC and nicotine, we explored whether e-cigarette users' risk for past 12-month NSSI varied by type of substance inhaled: nicotine, THC, or e-liquid believed to be substance-free (i.e., "just flavoring"). Importantly, vaping THC, but not nicotine, increased the risk for NSSI relative to vaping e-liquids containing flavoring only, again while controlling for demographic characteristics, affective symptoms, and other substances used. In this fully adjusted model, younger age, depression, and anxiety symptoms increased the risk for NSSI more than 2-fold to nearly 3 times the risk, though vaping THC and the use of conventional tobacco products or other substances continued to contribute to risk for self-injurious behavior. Clinicians treating college populations should consider screening students not only for e-cigarette use but also, for the specific types of liquids utilized in their vaping device.

Finally, we predicted frequent NSSI, which we defined as self-injurious behavior occurring 2 or more times each month over the past year. Contrary to our hypothesis, e-cigarette use decreased the risk for frequent NSSI in all four models. Interestingly, other substance use behavior did not affect the risk for frequent NSSI, though depression and anxiety increased the odds of frequent self-injurious behavior as expected. Although the temporal relationship between NSSI and substance use was unable to be assessed in the current study, a prior investigation of first-year college and university students suggested that the onset of a substance use disorder occurred more frequently after the onset of NSSI, compared to before NSSI onset (28). Thus, additional research on the motivations for e-cigarette use and the timing of use in relation to NSSI is necessary to advance the clinical relevance of future work in this field.

It is clear that young adult college students who are female, White, experience heightened symptoms of depression or anxiety; those who also engage in vaping, smoking, and other drug use are at increased risk for non-suicidal self-injurious behavior. Given our large sample size, we were also able to distinguish between nicotine and THC vaping and to individually calculate increased risk by type of liquid vaped. Uniquely, we found the risk increased among those who vaped THC, not nicotine, compared to flavor alone. This type of analysis is rare and will need to be replicated in future investigations given that most studies have not distinguished the type of liquid vaped when considering e-cigarette use and a risk factor for other health behaviors.

Despite its clinical salience, several limitations were present in this study. First, this work only assessed young adults who attended university or college in selected, participating U.S. academic institutions; this limits the generalizability of these findings and raises the potential of selection bias Second, the response rate was low; however, it is typical of online surveys all of which are subject to potential non-response bias. Non-response weights were applied to account for known characteristics, but other differences might not have been captured. Third, there may also be unaccounted psychosocial factors that confound the observed association between vaping and NSSI. Fourth, we were limited by the answer formats in vaping, smoking, and other substance use patterns. It would have been preferable to be able to distinguish those who smoked cigarettes every day, for instance, from those who smoked once a month. We were only able to distinguish those who reported smoking from those who reported no smoking. Fifth, these analyses did not explore associations between NSSI and different e-cigarette use patterns, including the dose, frequency, and mixing of e-cigarette flavors. Finally, non-suicidal self-injurious behaviors were not measured via a validated and reliable questionnaire that focuses on NSSI-related behaviors. Nevertheless, the Healthy Minds Study provides one of the largest, most representative surveys of college student mental health and behavior.

Future work is necessary to validate the association between e-cigarette use and NSSI behavior, to further examine other influences on this association, and to quantify the influence of dosage, frequency, and specific substance vaped. Indeed, it will be important to distinguish the type of liquid vaped and the frequency of self-harming behavior to maximize the utility of prevention programs and interventions among youth. Overall, our findings expanded scientific knowledge on the relationship between increasingly common substance use behaviors, such as e-cigarette use, NSSI, and suicidal ideation; this may aid in the identification of individuals who may benefit from tailored services and resources. As such, this research may help inform intervention and harm reduction efforts.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Healthy Minds https://healthymindsnetwork.org/research/data-for-researchers/.

Ethics statement

The University of Michigan's Health Sciences and Behavioral Sciences IRB approved the Healthy Minds study. All participants gave informed consent. Secondary analysis based on the publicly available data was approved by the University of Florida Institutional Review Board.

Author contributions

CS conceptualized the study, guided the analysis and wrote the first draft of the discussion, edited and rewrote other sections, and approved the final manuscript. SN assisted with the conceptualization of the study, conducted the analysis, wrote the first draft of the Introduction, Methods, and Results, and revised the final manuscript. CH made substantial revisions and edits to the manuscript. All authors approved the final version of this paper.

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Conflict of interest

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

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Nomenclature

NSSI: Non-suicidal self-injury;
THC: Tetrahydrocannabinol.

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Integrated hepatitis C treatment is associated with improved retention and success in outpatient treatment for opioid use disorder at a private clinic

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Background: Direct acting antiretrovirals (DAA) are effective for individuals who are infected with chronic hepatitis C virus (HCV), yet many people go without access to these lifesaving treatments.

Materials and methods: We conducted a non-randomized study evaluating treatment data for patients in outpatient treatment for opioid use disorder (OUD) at a private clinic. Patients who were HCV-positive, had been in OUD treatment for at least 4 weeks, and engaged in integrated HCV treatment with DAA (co-located within their treatment for OUD) were compared to patients with HCV who only received OUD treatment. We evaluated HCV cure; OUD medication adherence, treatment utilization and retention; and illicit substance use for those engaged in treatment between 9/2016 and 1/2018.

Results: Seventy-four patients completed integrated HCV-OUD treatment with DAA, with 87.8% achieving cure. Of the 66 who completed treatment and were subsequently evaluated for sustained viral response 98.5% were cured. Patients who received integrated HCV and OUD treatment in our clinic, stayed in OUD treatment longer, demonstrated higher OUD medication adherence, and used less opioids or cocaine compared to HCV-infected patients ($n = 572$) being treated only for OUD.

Discussion: We have reported on a reproducible intervention that lends itself to outpatient OUD treatment. Analyses demonstrate the potential positive impact HCV treatment has on OUD recovery, including reduction in opioid and cocaine use and increased retention in care

Conclusion: Co-locating HCV treatment with existing OUD treatment is feasible, effective, and demonstrates positive outcomes for the treatment of both conditions.

KEYWORDS

hepatitis C infection, opioid use disorder, direct acting antiretrovirals, integrated care, addiction medicine

Introduction

Chronic hepatitis C virus (HCV) infection is a major public health problem in the United States. A leading cause of cirrhosis and hepatocellular carcinoma, its mortality rate has been estimated at over 35% (1). The majority of the estimated 3.5 million Americans with chronic infected HCV are unaware of their infection (2). The current primary risk factor for HCV acquisition is injection drug use; 84% of cases with risk factor data in 2014 were among persons who inject drugs (PWID) (3). Increases in injection drug use have led to a 6-fold increase in new cases of HCV among persons 20–39 years old, from 2004 to 2018 (4). Morbidity and mortality associated with HCV proportionately impacts the lives of current and former PWID.

Direct acting antiviral (DAA) regimens for chronic HCV are safe and efficacious (5). They have revolutionized our ability to cure patients with chronic HCV infection. In addition to prevention of transmission and progression of liver disease, patients cured of HCV have decreased risk of diabetes, stroke, and improved cognitive function (6–8). Successful DAA therapy is also associated with significant improvements in objective and subjective measures of quality of life (9, 10). Despite the availability of DAA, the majority of PWID are not being treated (11) and only a small percentage know that newer treatments are highly effective with few side effects (12). Even when many patients in opioid use disorder (OUD) treatment are screened, it can be difficult to arrange successful treatment (11). Identifying and implementing interventions that reduce or eliminate barriers to HCV treatment is critical if we are to achieve the World Health Organization goal of eliminating HCV globally by 2030 (13).

PWID and their HCV infections, inextricably linked, are stigmatized and discriminated against, resulting in mistrust of medical providers and establishments (14–16). Patients and providers alike harbor misperceptions about whether abstinence is needed for treatment (17, 18). Initiatives aimed at overcoming these barriers in order to screen and treat PWID are vital in both treating the individual patient and reducing further transmission to stem this epidemic (19, 20). National organizations support treatment of PWID, with or without active substance uses (5, 21). Studies support high rates of sustained virological response (SVR) in people who are in recovery with opioid agonist treatment (17, 22) and those who are not, including those with active opioid use (23).

Co-location of HCV treatment together with addiction treatment, as recommended by the American Society of Addiction Medicine, eliminates additional referral (24). Patients are cared for by a trusted provider, avoiding potential stigma. We have begun integrating HCV treatment in our outpatient treatment for OUD services (25). To our knowledge, we are among the first commercial outpatient OUD treatment clinic to provide HCV treatment directly to patients in OUD treatment rather than referring them to primary or other specialist care. The purpose of this analysis is to evaluate the relationships between integrated HCV treatment on patients' HCV status and their OUD treatment.

Materials and methods

Study design

We conducted a non-randomized study using de-identified data from the electronic health record of patients being treated with medication for opioid use disorder (MOUD) in an outpatient treatment program in New Bedford, MA. Patients who received integrated treatment for their chronic HCV were compared with those who have not yet been treated to examine recovery outcome measures: treatment retention and utilization, medication adherence, and substance use. This research was reviewed by the Institutional Review Board at Northeastern University and deemed as not human subjects' research.

Setting

CleanSlate Outpatient Addiction Medicine, is a national company of free-standing, outpatient addiction treatment centers. CleanSlate Outpatient Addiction Medicine provides medication treatment for disorders of opioid and alcohol use. All patients initiating substance use treatment are screened for blood-borne pathogens at their initial visit including Hepatitis B virus, HIV, and HCV testing with reflex HCV ribonucleic acid polymerase chain reaction and genotyping for all HCV antibody-positive specimens. All [Treatment Program] providers are trained in pre- and post-test counseling, including educating patients about HCV DAA therapy.

Intervention

Beginning on 9/1/2016, patients with evidence of chronic HCV (i.e., viremic) who were adherent to their OUD treatment, operationalized as attending scheduled clinic visits with a medical provider, for at least 4 weeks (to increase probability of adherence to HCV medication, abstinence from illicit substances was not required) were offered HCV treatment on site at CleanSlate Outpatient Addiction Medicine in New Bedford, MA. Exclusion criteria included co-infection with HIV or hepatitis B, or unstable psychiatric disorder that would impair a patient's ability to adhere to the regimen. Interested patients were evaluated, those with signs or symptoms of decompensated cirrhosis or significant drug-drug interactions were referred to a hepatologist for treatment. Eligible candidates were started on DAA treatment by an advanced practice nurse who was trained to provide HCV treatment to existing OUD patients.

The practitioner completed 40 h of online training and one in-person training session (8 h) with an infectious disease specialist. Throughout treatment, supervision was provided by an addiction medicine/infectious disease specialist. All treatment regimens were determined in accordance with guidelines approved by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (5). The patients returned for one additional visit once their medications arrived at the clinic, to initiate treatment, during which side effects and the importance of adherence was reviewed. Once DAA treatment was initiated, patients' course of HCV care was monitored during their standard OUD visits.

Sample

The treatment group consisted of 74 patients (71.6% men) with HCV who received treatment with DAA as part of their treatment for OUD at an office-based medication treatment program. They are being compared to 572 other patients with chronic HCV who were receiving outpatient treatment with MOUD at the same office-based treatment program. The control group met the inclusion criteria for the intervention (viremic, without HBV or HIV, and attended OUD treatment visits with their provider for at least 4 weeks), but did not have a visit with the HCV NP during the period of the pilot either by choice or limited capacity of a single provider.

Study outcomes

To examine the relationships between integrated OUD/HCV treatment intervention on both HCV and OUD outcomes, differences between the two groups were evaluated. Response to HCV treatment was determined by HCV viral load 12-weeks post completion of treatment, sustained viral response (SVR).

Outcomes included OUD treatment utilization and retention, and substance use. Several variables were used to measure OUD treatment utilization: total time in care, time since the last visit, number of maintenance visits, and number of "re-join visits." If the time since the last visit was substantial, the patient might also be required to "re-join" the program. According to OUD treatment protocol, patients were required to come to the clinic for scheduled maintenance visits. Treatment retention was defined as retained or not retained (dichotomous yes/no) based on the patient's status as of January 2018.

To measure medication utilization, the total number of urine drug screens, which are performed at each clinic visit, frequency of which is determined by patients' stage of recovery, that were positive for buprenorphine was divided by the total number buprenorphine urine drug screen tests performed for each patient. The value resulted in the percentage of positive buprenorphine tests. Higher values indicated higher rates of appropriate medication utilization. To measure substance use, a similar percent positive value was obtained for urine drug screens results from each of the following drug categories: alcohol, amphetamines, benzodiazepines, cocaine, all other illicit opioids, and THC.

Data analysis

Patient characteristics between groups were compared using a paired *t*-test (age) and chi square analysis (gender). Between group differences of retention in treatment was evaluated using logistic regression. Between group differences in all remaining continuous outcomes were measured by ANCOVA (univariate, general linear model). Patient age and gender were included as covariates in all models. Race and ethnicity were not included as covariates in the regression model due to missing data (race % missing = 30.7; ethnicity % missing = 24.5). Available data indicates the sample is homogenous (94.4% White; 88.5% non-Hispanic). All analyses were conducted in SPSS v. 25 (26).

Because an individual who was in care for a longer duration would have higher values for many of the variables examined, regardless of care engagement, the treatment utilization variables and number of rejoin and maintenance visits were adjusted by the total time in care. Total time in care was measured as all time as represented in the electronic medical record. This included from each patient's initial visit to the end of their care episode or the end of the data collection time.

Results

Patient characteristics

All patients included in the analyses ($N = 646$) met criteria for HCV treatment; 74 received the OUD/HCV integrated treatment intervention. Mean patient age for all participants was 39.0 ($SD = 10.2$, range = 21.0–67.9). There was no difference in age ($t = -1.6$, $df = 643$, $p = 0.203$) or gender ($\chi^2 = 2.8$, $df = 1$, $p = 0.094$) between groups.

HCV results

Over half the patients treated for HCV were genotype 1 (55.4%, $n = 41$) and about a third (33.8%, $n = 25$) were genotype 3. The remainder were genotype 4 (8.1%, $n = 6$) or 2 (2.7%, $n = 2$). Figure 1 highlights patients' progression through treatment. Nearly all (97.3%) who initiated

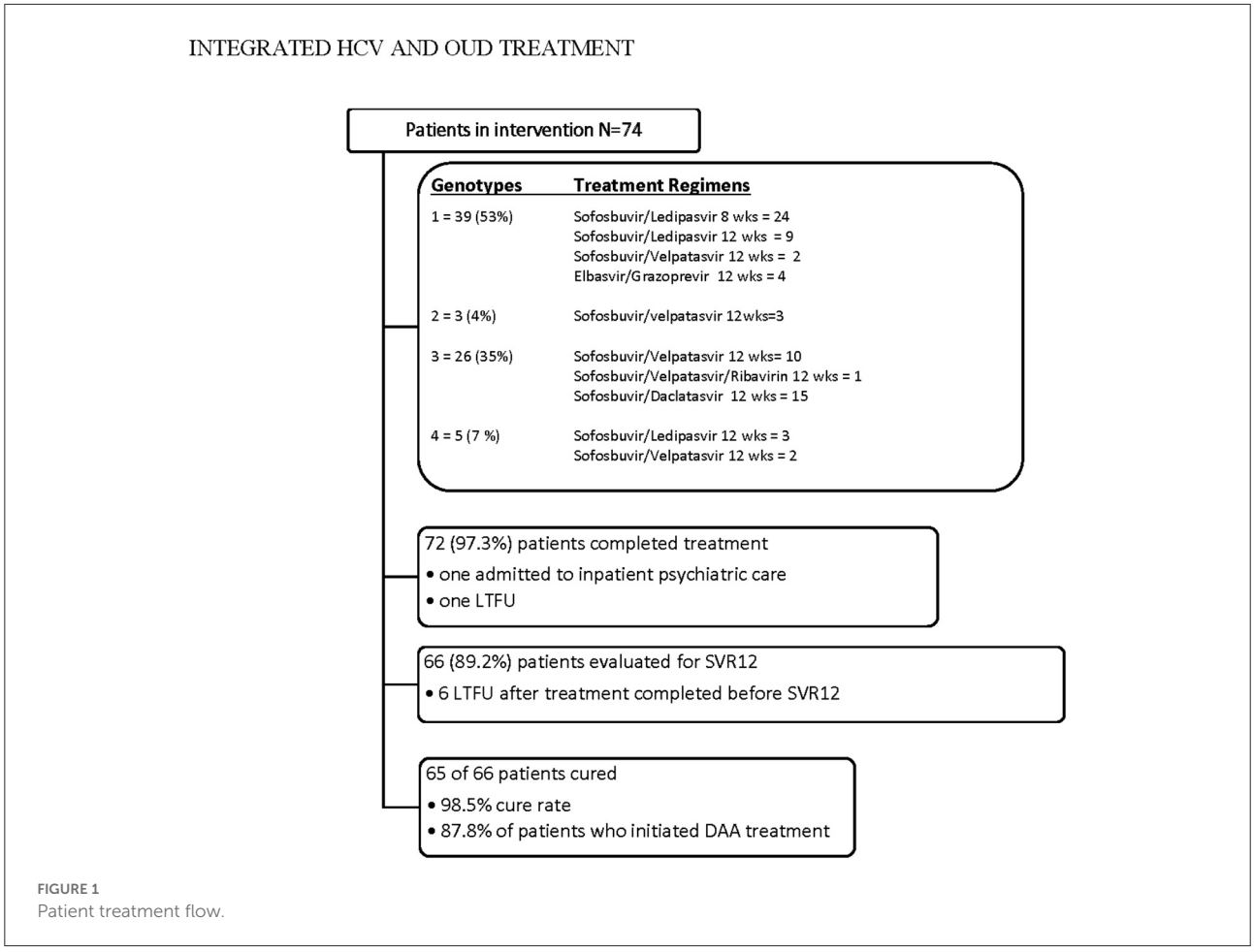

FIGURE 1
Patient treatment flow.

DAA treatment completed treatment. Six of the patients who completed treatment were lost to follow-up prior to SVR assessment. Among the 66 patients for whom SVR post-treatment data are available, all but one (98.5%) achieved cure. When considering all patients who initiated DAA treatment, 87.8% ($n = 65$) achieved cure. No patients in the treatment group stopped HCV treatment due to side effects or adverse effects.

OUD results

Patients receiving integrated HCV treatment (treatment) had higher rates of OUD treatment utilization, attended more OUD maintenance visits, and were in OUD treatment for a longer duration than patients receiving MOUD alone (control). Patients in the treatment group had less time since their last visit and fewer rejoin visits than those in the control group. There was no significant difference in adherence to buprenorphine for those in treatment group compared to the control group.

Substance use

After adjusting for covariates (age and gender), patients in the intervention group had lower rates of opioid and cocaine use. Notably, there was no difference in alcohol, THC, benzodiazepine, or amphetamine use (See Table 1).

Treatment retention

Analyses were performed to examine the relationship between intervention groups and patient retention. A patient was considered retained if they were a patient at the end of the data collection period. The logistic regression model predicting treatment retention was significant ($p < 0.001$) and 18.2% of the variance was explained (Nagelkerke R^2). The relationship between the intervention groups and treatment retention was statistically significant after covariate control ($B = 2.6$, $p < 0.001$). Patients who received integrated OUD/HCV treatment were 13.4 times (OR; 95% CI = 7.1–25.3) more likely to be retained in care with MOUD than patients who

TABLE 1 OUD treatment utilization, medication utilization, and substance use by treatment group[a].

	Treatment group					
	Control		Intervention			
	Mean	Standard error	Mean	Standard error	*F*	*p*
Treatment utilization						
Total time in care (years)	1.0	0.05	2.1	0.13	67.2	<0.001
Time since last visit (years)	1.1	0.03	0.3	0.09	74.9	<0.001
# rejoin visits	0.7	0.04	0.4	0.12	4.8	0.029
# maintenance visits	30.7	0.69	37.2	2.00	9.4	0.002
Medication utilization[†]						
Buprenorphine	82.2	1.1	87.5	3.2	2.4	0.119
Substance use[†]						
Alcohol	14.3	1.0	15.2	2.2	0.1	0.770
Amphetamines	5.0	0.6	5.9	1.8	0.2	0.637
Benzodiazepines	11.3	0.8	11.9	2.3	0.6	0.809
Cocaine	20.8	1.2	10.1	3.3	9.7	0.002
Opioids	14.6	0.7	5.2	1.9	21.1	<0.001
THC	34.5	1.7	28.5	4.6	1.5	0.222

[a]All analyses control for age and gender.
[†]Percent positive tests.

were not in the intervention group. Neither gender nor age were significantly related to retention ($B = 0.3$, $p = 0.174$ and $B = 0.01$, $p = 0.456$, respectively).

Discussion

Despite carrying the highest burden of HCV infection, fewer than 10% of PWID evaluated for HCV subsequently initiate treatment (17). Barriers to diagnosis and treatment of PWID impede linkage to care (27, 28). Our analyses demonstrate that the integration of HCV diagnostic and treatment services in outpatient OUD treatment overcomes some of the barriers and stigma that have historically impeded PWID accessing and completing treatment. Consistent with reported literature, when receiving HCV treatment integrated with MOUD, patients achieve SVR (cure rates) comparable to non-drug users (17, 28). Our setting, a commercial clinic for outpatient treatment of OUD, is novel, and addresses the need for treatment settings to provide more comprehensive services (29), including HCV testing. To our knowledge we are the first in the US to report integration of HCV care within this setting. This innovative approach broadens access to HCV treatment for this heavily affected yet underserved population, and has the potential to reduce morbidity and mortality, decrease health care expenditures, and stem transmission among high-risk individuals (9, 19, 20). Our evidence also builds on prior literature of high HCV cure rates with co-located HCV treatment provided in other opioid treatment programs (e.g., methadone clinics) (28, 29).

Non-clinical benefits for patients cured of HCV include improved quality of life and sense of wellbeing (30). Patients with OUD treated in the interferon era reported reduction in substance use-and return to "normality" as a result of curing their HCV (30, 31). Our analyses of patients with OUD who received integrated care with DAA in our clinic, builds on this literature, providing an objective assessment of measures of utilization of addiction care and indices of recovery. Notably, patients treated for HCV in our clinic were more adherent to all visit types.

We observed lower rates of opioid and cocaine use in the intervention group. However, despite the trend toward improved buprenorphine adherence in the intervention group, the difference was not significant, suggesting that the decline in use of illicit opioids and cocaine was not solely attributable to better buprenorphine utilization, which is consistent with prior literature (31). The significantly lower rate of cocaine use in the intervention group may be related to the decreased chronic fatigue and increased energy patients cured of HCV report (32), removing the need for cocaine's stimulating qualities. Prior qualitative work suggests being cured of HCV may alleviate internal stigma and catalyze improved self-care, resulting in reduced opioid and cocaine use (31). One

patient in this sample cured of HCV told their provider PL,

> *"… It's out of my body. I don't feel dirty anymore. I feel better, like I've accomplished a big step in my recovery … getting rid of the past. It's the last part of the guilt and stigma around injecting."*

Especially encouraging is the significant association of HCV treatment with higher utilization and better retention in OUD treatment when controlling for time in care. Previous research has identified HCV infection as factor impeding long-term treatment retention (33). Engaging and retaining patients in treatment with MOUD decreases mortality and is associated with a more durable and safer recovery (34). Improved retention in the treatment group could be due to pre-existing clinical relationships based on trust, which may act as an antidote to the sequelae of stigma (33). It is also possible that providing HCV treatment was the mechanism that engendered trust and a stronger connection, resulting in increased retention.

Limitations

Inclusion and exclusion criteria (e.g., being stable in care for 4 weeks and severe mental illness, respectively), were stricter than current recommendations for treatment of HCV. Indeed, more recent research has identified similar SVR outcomes in a patient population with high rates of mental illness and the presence of continued opioid use (17, 22, 23, 35). Our study utilized a retrospective design. While being treated for HCV was associated with less illicit substance use and higher retention rates in care, a prospective study design would be needed to assess whether there is a causal relationship. Our investigation was also limited to a single site and a homogenous patient demographic. In the site that provided the intervention, eligible participants were offered the opportunity to meet with the HCV NP based on the single provider's capacity. How many people were offered the opportunity and reasons for any decline to participate were not recorded. These data should be recorded in future studies to understand the uptake of integrated treatment and potential barriers to participation. It is possible that individuals who chose to participate in this intervention could be different than those who declined to participate in the intervention. Future research should include baseline comparison of social and medical constructs. There were significant missing data regarding race and ethnicity in the electronic health record, so we do not know the extent to which this sample mirrors general population of people affected by OUD and HCV. There were, however, no differences between groups based on age, gender, or race (among patients for whom racial identity is available). Still, the results should be interpreted with caution, and may not be generalizable to racial and ethnic minority subgroups. Finally, only a few patients were being treated with naltrexone for extended-release injectable, so comparisons between naltrexone and buprenorphine could not be made. Though the study provided a real-world patient experience, a future multi-site study could allow for a more diverse sample of participants, including those being treated with medications for opioid use disorder other than buprenorphine (e.g., methadone, naltrexone) and other preparations of buprenorphine (i.e., injectable).

Implications

This study of HCV treatment integrated within a commercial outpatient opioid treatment clinic has significant potential implications for the health system and policy. Efforts to achieve an 80% reduction in HCV globally by 2030 (13) will fall short unless screening and treatment of individuals seeking care for OUD is policy focus. Even an incremental increase (10%) in HCV treatment with DAA in areas with typical HCV prevalence (60%), has the potential to make a dramatic impact (20). Our treatment model was carried out by an advanced practice registered nurse with additional training specific to the treatment of HCV, which is currently not an option in every state. Simpler treatment algorithms since the introduction of DAA have made it more feasible for advanced practice registered nurses, physician's assistants, pharmacists, and those outside of specialty care (e.g., primary care) to provide treatment for HCV (36, 37). Similarly, patients face administrative barriers such as lengthy prior authorization procedures (29), sobriety requirements, and limitations on the number of treatment courses covered (37); easing these unnecessary restrictions would increase access to care.

We have reported on a reproducible intervention that lends itself to other outpatient treatment settings. Our analyses have demonstrated the potential positive that integrated HCV treatment may have on patient recovery, including reduction in illicit opioid use, reduced cocaine use, and increased retention in OUD care. Based on these data, HCV care is being expanded to 72 additional [*Treatment Program*] sites across 10 states within our national network of outpatient addiction clinics, and we encourage other treatment clinics to consider offering integrated HCV and MOUD treatments as well.

Conclusion

Treating and curing HCV in patients seeking care for OUD is vital to achieving elimination of HCV. These data suggest that scaling up integration of HCV treatment in a commercial outpatient OUD treatment clinic is feasible, effective and may improve recovery outcomes.

Data availability statement

The datasets presented in this article are not readily available because data for this study cannot be shared as it has been obtained from an outpatient OUD treatment organization that has restricted any further sharing of the data. Additional information on use of the data should be directed to LC, lchiodo@addictionref.org. Requests to access the datasets should be directed to lchiodo@addictionref.org.

Ethics statement

The protocol was reviewed at Northeastern University and deemed not human subjects research.

Author contributions

PL, SM, and AW conceptualized the study and participated in writing and revision of the manuscript. PL implemented the intervention. LC and JB conducted statistical analysis and interpretation and participated in writing and revision of the manuscript. All authors have reviewed and approved the submitted manuscript.

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Conflict of interest

PL is employed by CleanSlate Outpatient Addiction Medicine and receives speaker's fees from Gilead Sciences, Inc. AW has equity in CleanSlate Outpatient Addiction Medicine.

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

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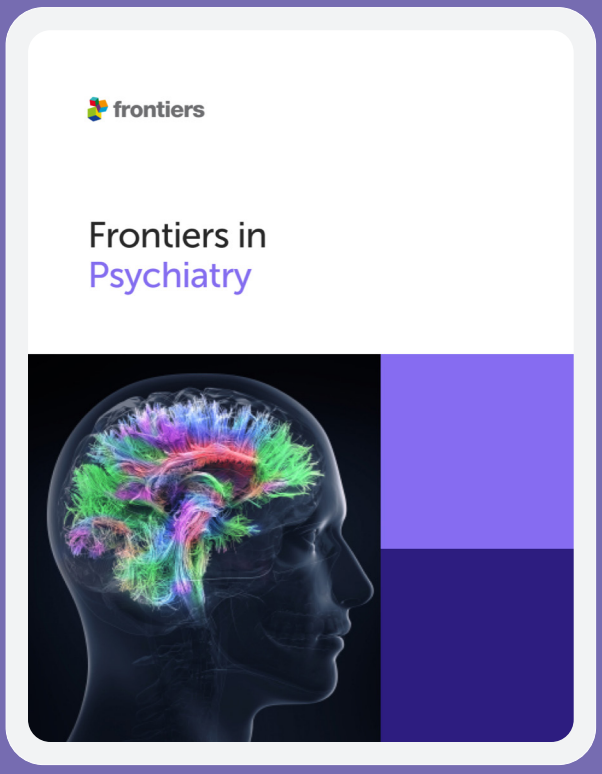

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