SUBSTANCE USE AND THE PSYCHOSIS SPECTRUM

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SUBSTANCE USE AND THE PSYCHOSIS SPECTRUM

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Editorial: Substance use and the psychosis spectrum

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Editorial on the Research Topic
Substance use and the psychosis spectrum

Introduction

Substance use rates have alarming trends of increase throughout the world (1). A recent multicentre study shows that the variation in substance use contributes to the variation in the incidence of psychotic disorders across different regions (2). Substance use is one of the most important modifiable risk factors for psychosis, which highlights the importance of research on the association between substance use and psychosis (3, 4). However, many questions on this association remain unanswered. In this article collection, we bring together some novel evidence from clinical, neurobiological as well as therapeutic perspectives.

Papers in this Research Topic

Chang et al., present a cross-sectional study including 397 schizophrenia and related psychoses patients from a tertiary psychiatric hospital in Singapore. One in tenth of the patients reported problematic drug and/or alcohol use. This rate is relatively lower than the rates reported in western countries (1, 2). However, problematic drug/alcohol use is associated with greater mental distress and poor physical health in psychosis spectrum patients, in line with substantial evidence from different parts of the world (3–8).

To date, a considerable number of longitudinal studies have been conducted to elucidate the associations between substance use and psychosis (9–11). However, evidence on momentary dynamic associations between substance use and psychosis in daily life is scant.

Weiss et al. present an interesting study using the experience-sampling methodology (ESM). In this study, youth with clinical high risk (CHR) or early psychosis (EP) provided data on substance use, psychotic symptoms, and negative affect six times a day *via* a smartphone application. Results showed that substance use was significantly associated with lagged negative affect. With relatively larger sample sizes and longer follow-up periods, ESM seems to be a promising tool to provide insight into moment-to-moment associations between substance use and psychosis.

Over the last two decades, clinicians struggle with the increased incidence of methamphetamine and ketamine induced psychoses across the world (12–14). However, our insight into this relatively "recent" crisis is limited. Luo et al. compared different features of psychotic symptoms between users of these drugs (n = 842). After at least two weeks of drug abstinence, psychotic symptoms were reported by three quarters of methamphetamine use disorder (MUD) patients and half of ketamine use disorder (KUD) patients. MUD patients were more likely to experience positive psychotic symptoms, as well as stereotyped thinking, difficulty in abstraction withdrawal, and poor rapport than KUD patients, whereas general symptoms, such as sleep and anxiety, were similar across the two groups.

This article collection includes novel studies on the neurobiological underpinnings of substance use-psychosis comorbidity. Johnstone et al. systematically reviewed the evidence on the clinical utility of neuromodulation techniques to treat comorbid substance use and psychosis spectrum disorder. Authors concluded that preliminary evidence supported the effectiveness of repetitive transcranial magnetic stimulation (rTMS) targeting the dorsolateral prefrontal cortex (DLPFC), a well-known brain region involved in top-down regulation, on reducing cannabis and tobacco use in patients with schizophrenia and schizoaffective disorder. However, some studies showed no significant effect of rTMS on reducing cannabis and tobacco use in this population, as also presented by Ward, Brady et al. in their mini review. An original fMRI study by Ward, Beermann et al. showed that nicotine use might normalize default mode network hyperconnectivity in patients with schizophrenia. Default mode network hyperconnectivity was previously associated with impaired attention. Considering the plausible unique pro-cognitive effect of nicotine use in patients with schizophrenia, this article suggested targeting the default mode network hyperconnectivity for smoking cessation in schizophrenia patients. Finally, Hau et al. presented a brief research report demonstrating a positive or borderline result of anti-neuronal autoantibodies in one-third of synthetic cannabinoid-induced psychosis patients. However, no significant association was found between PANSS scores and the presence of anti-neural antibodies in this study. These results require replication in larger samples.

One of the major challenges in psychiatry is the relatively low treatment adherence in patients with comorbid substance use disorders and psychosis spectrum disorder. Bouchard et al. present a comprehensive systematic review and meta-analysis of available evidence for dropout rates in psychosocial interventions for this population. Results showed that more than a quarter of these patients dropped out from psychosocial treatments with even higher rates among patients with stimulant use disorder. Long acting injectable antipsychotics (LAIs) might help cope with high drop-out rates. Coles et al. presented a systematic review of the literature investigating the use of LAIs in this population. Preliminary evidence suggests that LAIs might be safe, well tolerated, and mostly effective in the treatment of psychosis spectrum and substance use comorbidity. Furthermore, Gjerde et al. presented an original study demonstrating that cannabis use in patients with first treatment psychosis was not significantly associated with negative beliefs about antipsychotic medication. This preliminary result suggests that favorable treatment adherence may be achieved in comorbid psychosis spectrum and substance use disorder patients, if other reasons for non-adherence (e.g., lack of insight, side effects) are taken into account.

Challenges and future directions

Substance use may be an excellent target for primary, indicated and selective prevention strategies for psychosis. However, there exist questions that await urgent answers to move the field forward. First, evidence on the causal link between substance use and different domains of psychosis (i.e., positive, negative, disorganization and affective) should be established in replication studies. Studies should also evaluate the possible influence of psychosis on substance use (i.e., reverse causality) by using genetically informed approaches, such as Mendelian randomisation analyses (15). Second, novel evidence for methods to intervene in substance use in individuals at high risk for psychotic disorders is needed. Third, insight on the link between excessive alcohol use and psychosis need to be clarified. Finally, urgent evidence on the role of different classes of substances (e.g., novel stimulants, gabapentinoids etc.) for inducing psychosis is needed. In summary, a clearer insight into the clinical and neurobiological basis of the link between substance use and psychosis warrant longitudinal studies with frequent follow-ups with shorter time gap between each visit and granular assessments that take into account genetic risk and environmental factors at both individual and neighborhood-based levels. We hope that this collection of interesting articles may draw scientific attention to this growing public health crisis (16).

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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Problematic Drug Use Among Outpatients With Schizophrenia and Related Psychoses

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Background: Problematic drug use is common among psychiatric patients and is linked with poorer course and outcomes of illness. The aim of this study is to assess the prevalence of problematic drug use, and to explore its sociodemographic correlates and associations with health behaviors and outcomes among outpatients with schizophrenia and related psychoses in Singapore.

Methods: Data from 397 individuals who were aged 21–65 years and were seeking treatment for schizophrenia and related psychoses in the outpatient clinics of a tertiary psychiatric hospital were analyzed. The Drug Abuse Screening Test (DAST-10) was used to assess problematic drug use. Information on sociodemographics, smoking status, alcohol use, symptoms severity and quality of life were collected. Multivariable logistic regressions were conducted to explore correlates and associations of problematic drug use.

Results: The prevalence of problematic drug use was 5.8% ($n = 23$) in the sample, and 10.6% ($n = 42$) of the participants reported having problematic drug use and/or problematic alcohol use. More males than females reported having problematic drug use ($p = 0.021$), and also problematic drug and/or alcohol use ($p = 0.004$). Significant associations were observed between problematic drug use and smokers with nicotine dependence, and with physical health domain of quality of life. Individuals with greater symptom severity were approximately twice as likely to have problematic drug use and/or alcohol use.

Conclusion: While the prevalence of problematic drug use in this sample population is relatively lower compared to other countries, there is a considerable number who might be at risk. Routine screening and close monitoring of drug use is recommended as part of psychiatric assessment, particularly among males and patients with nicotine dependence.

Keywords: drug misuse, drug use, schizophrenia, DAST, substance misuse

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INTRODUCTION

Drug use is common among individuals with schizophrenia. The rate of comorbid substance use disorder in persons with schizophrenia ranges widely between 10 and 70%, with variations largely attributed to methodological differences such as study population and variability in definitions of substance use (1). Data from the US Epidemiological Catchment Area Study showed that 47.0% of individuals with a lifetime diagnosis of schizophrenia or schizophreniform disorder met the criteria for any substance use (abuse and dependence), 27.5% met the criteria for any drug (other than alcohol) disorder, and 33.7% met criteria for an alcohol disorder (2). The odds of having these comorbid conditions were three to six times higher among those with schizophrenia as compared to the general population. A case-control study similarly reported higher number of patients with schizophrenia who had problem use of drugs and alcohol as compared to matched controls from the general population (3). More recently, a meta-analysis established a lifetime rate of cannabis use disorder at 27.1% among clinical samples of patients with schizophrenia (4). Drug use contributes to increased risk of psychosis (5) and while for some individuals such substance-induced psychosis could be a transient state, the clinical conditions could persist, mimicking the positive and negative symptoms observed in schizophrenia (6). The transition from substance-induced psychosis to primary psychotic disorder has been reported in the literature (7, 8).

Problematic use of drugs as discussed in this article generally refers to the use of drugs that resulted in physical, psychological, social and legal problems [for definitions, see Refs. (9) and (10)]. It has been linked with poorer course and outcomes for patients with schizophrenia. Drug abuse was a significant predictor of self-harm and suicide among those with schizophrenia (11, 12), and individuals with a dual diagnosis of substance use disorder and schizophrenia reported higher positive and negative symptoms, and were more likely to be medication non-compliant and depressed compared to those with a single diagnosis of schizophrenia (13). A longitudinal study among patients with recent onset of psychosis found that those with persistent use of cannabis had more positive symptoms and a continuous illness (i.e., no remission longer than 6 months) at follow-up (14). Furthermore, substance abuse in patients with schizophrenia was associated with increased rates of hospitalizations, incarceration and use of emergency services, as well as higher treatment expenditure (15, 16).

There is some evidence in the literature showing the effectiveness of treating drug-related problems among patients with a dual diagnosis of schizophrenia and substance use disorder (17–19). This included improvements in psychiatric outcomes in areas of global functioning, positive symptoms and quality of life, and in substance-related outcomes in terms of relapse and days abstinent. However, some studies have reported limited evidence on the effectiveness of psychosocial interventions (20, 21), and the absence of high-quality randomized controlled trials precluded definitive conclusions (22). Nonetheless, given the negative outcomes of substance use disorder in patients with schizophrenia and the potential improvement in outcomes with interventions, it remains important to identify the extent of problematic drug use in this population.

Singapore is a multi-ethnic city-state located in Southeast Asia with a resident population of 4.04 million (23). While the lifetime prevalence of schizophrenia and psychotic disorder in Singapore was established at 2.3% in the general population (24), little is known about the prevalence of problematic drug use among those with the condition. In the general population, the total number of individuals arrested for illicit drug use was 3,014 in 2020, a 15% drop from the previous year, and Methamphetamine remained the most commonly used drug (25). To date, only one study has been conducted in Singapore among patients with schizophrenia to examine substance abuse [alcohol and other substances; (26)], and two studies have examined hazardous alcohol use among patients with first episode psychosis, and among a mixed sample of outpatients with schizophrenia and depressive disorders (27, 28). Given the paucity of research particularly on drug use, this study was thus conducted with the aim to (i) establish the prevalence of problematic drug use in a clinical sample of patients with schizophrenia and related psychoses, (ii) identify sociodemographic correlates of problematic drug use, and (iii) explore associations between problematic drug use and smoking status, symptoms severity as well as quality of life.

METHODS

Study Design and Sample

The study utilized data collected from a cross-sectional study conducted at the Institute of Mental Health (IMH), a tertiary psychiatric hospital in Singapore. Recruitment of participants took place between October 2019 and March 2021, with a temporary suspension between April 2020 and June 2020 due to a nationwide lockdown in response to the COVID-19 pandemic. Face-to-face recruitment and data collection resumed after which, subsequent participants were given the option to complete the study online should they prefer. Participants were outpatients seeking treatment at IMH and were recruited through convenience sampling following referrals from clinicians and other mental healthcare professionals (e.g., case managers, researchers). They were invited to participate in the study if the following inclusion criteria were met: (1) Singapore citizens or permanent residents aged 21–65 years; (2) clinically diagnosed with schizophrenia or having related psychoses, as determined by a psychiatrist following the Diagnostic and Statistical Manual of Mental Disorders-IV (29) criteria; and (3) able to read and understand English. Prior to data collection, written informed consent was obtained from participants who were recruited face-to-face, while online electronic consent was taken from those who completed the study online. The study was approved by the relevant institutional ethics committee (National Healthcare Group Domain Specific Review Board).

Measures

Drug Abuse Screening Test (DAST)

The DAST-10 is a brief self-reported instrument to assess misuse of drugs, excluding alcohol and tobacco, in the past year (30).

Items were given a score of 1 for a "yes" response (except for Item 3 which is reversed scored, where "no" was given a score of 1) to questions related to maladaptive drug use behavior and its consequences (e.g., "Have you used drugs other than those required for medical reasons?"; "Have you neglected your family because of your use of drugs?"), and a total score was obtained by summing items across the scale. The total score can be interpreted as the degree of problematic drug use, with categories reflecting "none" (0), "low" (1–2), "moderate" (3–5), "substantial" (6–8) and "severe" (9–10) level of problems. For this study, a cut-off score of $\geq$3 was used to index significant problematic drug use as it has demonstrated high sensitivity and specificity in validation studies among psychiatric population (31, 32). The scale showed good internal consistency in this study sample with a Cronbach's alpha of 0.73.

Fagerstrom Test for Nicotine Dependence (FTND)

Information on smoking behavior was collected by first asking participants if they were current smokers. Those who responded "yes" proceeded to complete the 6-item FTND which assessed physiological dependence on tobacco smoking (33). Items in the scale were summed to yield a total score ranging from 0 to 10. Following studies conducted in the local general population and among psychiatric patients, a cut-off score of $\geq$5 was used to indicate nicotine dependence (34, 35). Participants were then classified as either "non-smokers," "smokers without nicotine dependence" or "smokers with nicotine dependence".

Cut-Annoyed-Guilty-Eye (CAGE)

The CAGE questionnaire uses four items to assess self-reported problems related to alcohol use (36). These items were prefaced by a screening question that asked "Was there ever a period in your life when you drank at least 12 drinks in a year?" Participants who answered "yes" to the screening question completed the four items in the CAGE tool regarding their drinking habits. Endorsing two or more items in the CAGE tool was indicative of problematic alcohol use in this study. Those who answered "no" to the screening or indicated that they had never drunk alcohol were directed to skip the CAGE questionnaire. Participants were thus classified as either "non-drinkers," "drinkers without problems" or "drinkers with problematic alcohol use." The tool has been validated (37) and has been used to examine alcohol consumption in the local population (38). A moderate internal consistency of this scale was obtained for this sample ($\alpha = 0.69$).

Symptoms Checklist-90-Revised (SCL-90-R)

The SCL-90-R is a widely used instrument that provides a measure of psychiatric distress and severity of psychopathology symptoms (39). The checklist consists of 90 items and respondents were asked to rate how much they were bothered by the symptoms in the past week using a five-point Likert scale from 0 = Not at all to 4 = Extremely. Total scores for nine primary symptom dimensions and three global measures of psychological distress can be obtained from the scale. The Global Severity Index (GSI) was calculated by taking the average of all items, with higher scores indicating greater distress and symptom severity. Internal consistency of the scale was high for the study sample ($\alpha = 0.99$).

World Health Organization Quality of Life-BREF (WHOQOL-BREF)

This 26-item instrument assesses subjective evaluation of personal health and well-being over the past 2 weeks using a 5-point Likert scale (40). It covers four domains: physical health, psychological health, social relationships, and environment. Domain scores were calculated by taking the mean score of items within each domain and multiplied by 4 to transform the value to a 4–20 scale; higher scores reflect greater satisfaction and higher QoL in the domain. The scale has previously been validated in Singapore and has obtained sound psychometric properties (41, 42).

Sociodemographic information including age, gender, ethnicity, highest educational attainment, marital status and monthly personal income [in Singapore dollars (SGD)] were collected.

Statistical Analysis

Descriptive analyses were performed to describe the participant profile. Mean and standard deviations were calculated for continuous variables, and frequencies and percentages were computed for categorical variables. In order to produce more reliable estimates, ethnicity was reclassified as Chinese vs. non-Chinese, and the "primary and below" and "secondary" categories for educational attainment were regrouped as a single category "secondary and below" for subsequent analyses. Independent *T*-test, Chi-square test and Fisher's exact test were conducted to explore sociodemographic correlates of problematic drug use at a bivariate level. Associations between problematic drug use and smoking status, symptoms severity and quality of life were assessed using multivariable logistic regression. Problematic drug use was treated as outcome variable and symptom severity, smoking status, and quality of life (all four domains) as independent variables. To improve stability of the model and its estimates, sociodemographic variables found to be significant in bivariate analyses were included in the regression model. Noting the relatively low prevalence of problematic drug use in this study sample, the same set of analyses were conducted to further examine correlates and associations with "problematic drug use and/or alcohol use" as the outcome variable. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA), except for Fisher's exact test which was conducted using Stata version 17, and statistical significance was set at p-value <0.05.

RESULTS

Sample Characteristics

A total of 400 participants were recruited for the study. However, three cases were excluded from analysis for the following reasons: (i) one person being enrolled twice in the study, (ii) one participant requested to withdraw from study, and (iii) one participant was above the age limit of the study. The final study sample consisted of 397 participants.

TABLE 1 | Profile of study sample ($n = 397$).

		n	%
Age (Mean, SD)		36.2, 10.9	
Gender	Female	196	49.4
	Male	201	50.6
Ethnicity[a]	Chinese	297	74.8
	Malay	51	12.8
	Indian	38	9.6
	Others	11	2.8
Educational attainment	Primary and below[b]	18	4.5
	Secondary[b]	120	30.2
	GCE "A" Level/Diploma/Vocational training	182	45.8
	Degree and above	77	19.4
Marital status	Single	320	80.6
	Married	47	11.8
	Separated/Divorced/Widowed	30	7.6
Monthly personal income[c]	No income	114	30.1
	Below S$2,000	202	53.3
	S$2,000–S$3,999	48	12.7
	S$4,000 and above	15	4.0
Problematic drug use[d]	None (0)	353	89.6
	Low (1–2)	18	4.6
	Moderate (3–5)	17	4.3
	Substantial (6–8)	5	1.3
	Severe (9–10)	1	0.3
Problematic alcohol use	Non-drinkers	347	87.4
	Drinkers without problems	29	7.3
	Drinkers with problematic alcohol use	21	5.3
Smoking status[c]	Non-smokers	307	78.3
	Smokers without nicotine dependence	31	7.9
	Smokers with nicotine dependence	54	13.8

[a] *Ethnicity was reclassified as Chinese vs. Non-Chinese for subsequent analyses.*
[b] *These two categories were regrouped as a single category for subsequent analyses.*
[c] *Remaining responses were "Refuse/Don't Know" and were treated as missing data. Valid percentages are presented.*
[d] *Numbers in bracket indicate respective range of DAST score. Valid percentages are shown after accounting for 3 missing data cases.*

The mean age of participants was 36.2 years (SD = 10.9; **Table 1**). There was an approximately equal number of male and female participants and the majority of them were Chinese (74.8%) and single (80.6%). The mean SCL-90-R Global Severity Index was 0.94 (SD = 0.9).

Prevalence of Problematic Drug Use and Its Correlates

The prevalence of problematic drug use (DAST-10 score ≥3) in this sample was 5.8% ($n = 23$; **Table 1**). Though not meeting the DAST-10 cut-off score, 4.6% of the participants had a low degree of problematic drug use. 5.3% ($n = 21$) of the study sample reported having drinking problems, and the prevalence of problematic drug use and/or alcohol use was 10.6% ($n = 42$).

Gender was the only significant correlate found to be associated with problematic drug use at bivariate level (males 8.5% vs. females 3.1%, $p = 0.021$; **Table 2**). There were also significantly more males than females (15.1 vs. 6.2%) who reported having problematic drug use and/or alcohol use ($p = 0.004$).

Associations With Smoking Status, Symptoms Severity and Quality of Life

Problematic drug use was significantly associated with smoking status. Compared to non-smokers, smokers with nicotine dependence were ∼5 times as likely to have problematic use of drugs (OR = 4.79, 95% CI: 1.57–14.61; **Table 3**). A higher score in physical health domain of quality of life was associated with lower odds of problematic drug use (OR = 0.65, 95% CI: 0.48–0.88), while a higher score in the environmental domain was associated with higher odds of problematic drug use (OR = 1.29, 95% CI: 1.01–1.65).

Similar associations were observed between problematic drug use and/or alcohol use and smoking status as well as quality of life. Smokers with nicotine dependence were ∼4 times as likely to have problematic drug use and/or alcohol use than non-smokers (OR = 3.81, 95% CI: 1.51–9.61). Higher score in the physical health domain of quality of life was associated with lower odds of problematic drug use and/or alcohol use (OR = 0.71, 95% CI: 0.57–0.90), and higher score in the environmental domain was associated with higher odds of problematic drug use and/or alcohol use (OR = 1.26, 95% CI: 1.03–1.53). Additionally, greater symptom severity was associated with increased odds of problematic drug use and/or alcohol use (OR = 1.89, 95% CI: 1.16–3.09).

DISCUSSION

The present study aimed to establish the prevalence of problematic drug use among patients with schizophrenia and related psychoses. It was found that 5.8% of patients surveyed in this study reported misusing drugs in the past 1 year, and 10.6% had problems with drug use and/or alcohol use. Notwithstanding the differences in study methodologies, our finding suggests that problematic drug use is less common among patients with schizophrenia in Singapore as compared to other countries (3, 4).

In general, the use of illicit drugs is lower in Singapore than most other countries, and this largely reflects Singapore's zero tolerance approach to drugs (43) and the success of anti-drug movement in the country. The Central Narcotics Bureau is the primary drug enforcement agency in Singapore and has four main strategies in place to keep the nation drug-free: preventive drug education, rigorous enforcement, treatment and rehabilitation, and aftercare and continued rehabilitation. These efforts are supported by other agencies including the Singapore Anti-Narcotics Association and the Yellow Ribbon Singapore. In the recent years, a rehabilitative and integrative approach toward individuals with drug related offenses has been embraced,

TABLE 2 | Sociodemographic correlates of problematic drug use and/or alcohol use.

		With problematic drug use (DAST-10 ≥3)			With problematic drug and/or alcohol use		
		Yes *n*	No *n*	*p*-value	Yes *n*	No *n*	*p*-value
Age (Mean)		35.7	36.1	0.838	36.2	36.1	0.933
Gender	Female	6 (3.1)	189 (96.9)	**0.021**	12 (6.2)	183 (93.8)	**0.004**
	Male	17 (8.5)	182 (91.5)		30 (15.1)	169 (84.9)	
Ethnicity	Chinese	17 (5.8)	278 (94.2)	0.913	29 (9.8)	266 (90.2)	0.357
	Non-Chinese	6 (6.1)	93 (93.9)		13 (13.1)	86 (86.9)	
Educational attainment	Secondary and below	8 (5.9)	128 (94.1)	0.753	16 (11.8)	120 (88.2)	0.870
	GCE "A" Level/ Diploma/Vocational training	12 (6.6)	169 (93.4)		18 (9.9)	163 (90.1)	
	Degree and above	3 (3.9)	74 (96.1)		8 (10.4)	69 (89.6)	
Marital status	Single	17 (5.4)	300 (94.6)	0.465	31 (9.8)	286 (90.2)	0.198
	Married	3 (6.4)	44 (93.6)		5 (10.6)	42 (89.4)	
	Separated/Divorced/Widowed	3 (10.0)	27 (90.0)		6 (20.0)	24 (80.0)	
Monthly personal income	No income	9 (8.1)	102 (91.9)	0.125	15 (13.5)	96 (86.5)	0.075
	Below S$2,000	8 (4.0)	194 (96.0)		17 (8.4)	185 (91.6)	
	S$2,000–S$3,999	1 (2.1)	47 (97.9)		3 (6.3)	45 (93.8)	
	S$4,000 and above	2 (13.3)	13 (86.7)		4 (26.7)	11 (73.3)	

Numbers in bracket represent row percentages. p-value obtained from T-test for continuous variable and Chi-square or Fisher's exact test for categorical variables. Significant values (p < 0.05) are bold.

TABLE 3 | Associations with smoking status, symptoms severity, and quality of life.

	Problematic drug use			Problematic drug and/or alcohol use		
		95% Confidence interval			95% Confidence interval	
	OR[a]	Lower bound	Upper bound	OR[a]	Lower bound	Upper bound
Smoking status						
Non-smokers	Reference			Reference		
Smokers without nicotine dependence	4.37	0.98	19.41	2.57	0.69	9.54
Smokers with nicotine dependence	**4.79**	1.57	14.61	**3.81**	1.51	9.61
Symptom severity						
Global Severity Index	1.36	0.74	2.51	**1.89**	1.16	3.09
Quality of life						
Physical health	**0.65**	0.48	0.88	**0.71**	0.57	0.90
Psychological health	1.14	0.88	1.47	1.11	0.91	1.35
Social relationship	0.99	0.82	1.20	0.95	0.82	1.10
Environment	**1.29**	1.01	1.65	**1.26**	1.03	1.53

[a]*Odds ratio derived from multivariable logistic regression controlled for gender. Results in bold indicate significant findings (p < 0.05).*

and through community-based programs where efforts in early reintegration of these individuals into the community are made (44). Nonetheless, some challenges may remain in drug control and treatment strategies such as a need to focus on familial interventions and more research in the area of drug addiction (45, 46).

Results from the study revealed a considerable number of patients with schizophrenia who may be at risk of significant problematic drug use. Though not meeting the threshold in this study to be classified as having significant problematic drug use, 4.6% of those surveyed had a low degree of problematic drug use (i.e., DAST-10 score: 1–2). It remains that this group should be closely monitored for their drug use and brief counseling may be recommended for them (47). Given that several reasons have been identified for illicit drug use among individuals with psychotic disorders, including social reasons and as coping mechanism for symptoms and side-effects of medications (48, 49), future studies can aim to explore drug use motivations

within this at-risk group to effectively intervene at an early stage. Furthermore, understanding the frequency and types of drugs used would be essential. In the local context, the study by Verma et al. (26) found that benzodiazepine was one of the frequently abused substances among patients with schizophrenia and the authors called for caution when prescribing these medications.

Consistent with studies in the literature which identified gender as a significant correlate of substance use (50–53), the current study found that more males than females had problematic drug use, and also problematic drug and/or alcohol use. Data from national statistics have shown that there were consistently more males than females who used illicit drugs in Singapore (54). Such a gender disparity could reflect differences in opportunity to use drug rather than vulnerability; males were found to have greater opportunities to use drug, but when once presented with the opportunity, females were as likely as males to initiate drug use (55). While the severity of substance use between both genders might be similar (56), females might be more susceptible to the negative effects of drugs use (57, 58) and also more likely to relapse following abstinence (59). Additionally, males and females with serious mental illness were found to differ in drug use behavior including ways to drugs access and reasons for drug use. Women were more likely to have drugs given to them by a significant other, and to report using drugs to test their ability to control drug use (60). In terms of hazardous alcohol use, several biological risk factors (e.g., genetic risks and gender differences in physiological effects of alcohol) and psychosocial risk factors (e.g., relating to social norms and general roles) have been proposed to account for the gender differences (61). These findings collectively suggest that effective treatment plans targeting problematic drug and alcohol use among patients with schizophrenia and related psychoses would need to consider such gender differences.

In line with studies that established the link between smoking and drug and alcohol use in patients with schizophrenia (62, 63) and also in the general population (64, 65), this study found that smoking behavior in patients with schizophrenia is significantly associated with problematic drug use. Smokers with nicotine dependence were five times more likely to have problematic drug use as compared to non-smokers, and four times more likely to have problematic drug use and/or alcohol use. These findings provided additional evidence of the close association between substance misuse and schizophrenia. Many hypotheses have been proposed to explain for this phenomenon, including common underlying genetic factors that predispose individuals to substance use behavior and schizophrenia, and also the self-medication hypothesis which suggests that patients use substance to cope with their psychiatric symptoms and the side-effects of medications (66). There also exist evidence for the gateway hypothesis which posits that smoking serves as a gateway substance to illicit drug use (67, 68). Given the high co-occurrence of problematic drug use and alcohol use along with nicotine dependence, it is recommended that routine assessments of nicotine use be conducted among patients with schizophrenia and related psychoses to closely evaluate for potential problems with drug use and alcohol use.

This study found that patients with greater symptoms severity were more likely to have problematic drug use and/or alcohol use. A study by Spencer et al. (69) similarly demonstrated symptoms severity as a significant predictor of cannabis or alcohol use among individuals with psychotic disorder, and this was mediated by their motives for using substances; worse symptoms resulted in stronger motives which in turn lead to stronger psychological dependence on substances. It may also be plausible that the problematic use of drug and alcohol contributed to greater symptoms severity. A study among older adults with schizophrenia found that higher levels of alcohol consumption was associated with higher levels of general psychopathology, and among them individuals with comorbid alcohol abuse had more severe negative symptoms and general psychopathology (70). Similarly, in a longitudinal study among persons with psychotic disorder, a reduction in the quantity of alcohol consumed predicted reduction in depressive symptoms, though not with anxiety nor psychotic symptoms (71). However, contradictory findings have been reported in the literature where some patients experienced symptom reduction (decreased anxiety and depression) following alcohol and cannabis use (72), which may in part be due to differences in the types of substance examined and study methodologies.

A significant negative association was observed between physical health domain of quality of life and problematic drug use and/or alcohol use. It may be plausible that patients who perceived poor health from the physical side effects of anti-psychotic medications used illicit drugs or alcohol to relieve such negative experiences (49, 73). It is equally plausible that poor health could be directly attributed to the consequences of misusing drugs (74). Prior studies have similarly reported poorer quality of life among patients with schizophrenia who were current substance users (75) and among those with current stimulant drug use (76). However, contrary to these findings, the study by Herman (77) found that inpatients with comorbid schizophrenia and substance abuse disorder reported better quality of life than those non-substance abusing inpatients. The author attributed this disparity to group differences in terms of lower levels of psychopathology and better executive functioning in the former group. Future studies may look into exploring these clinical variables in understanding the associations of problematic drug use in patients with schizophrenia and related psychoses.

There are a few limitations of this study to be considered when interpreting the results. Firstly, participant's self-reported data was used and thus the extent of problematic drug use could be underestimated due to social desirability bias. However, measures were taken to reduce such bias whereby participants were reassured regarding data confidentiality and were given the privacy to complete the questionnaire on their own. Next, the data collection period overlapped with the COVID-19 pandemic and the demand and supply of illicit drugs could have been affected due to movement restrictions across country borders. This might have influenced the availability and thus frequency of drug use among the study participants. The cross-sectional design of the study limits the ability to draw conclusions on the

causal effects of associations examined. Lastly, as participants recruited in this study were outpatients, findings may not be generalizable to inpatient setting where clinical profile of patients differs (e.g., severity of psychotic symptoms, higher comorbidity with substance use) and is likely to influence the prevalence and associations established in this study.

Despite its limitations, this study in many ways contributed to extant literature on problematic drug use among patients with schizophrenia and related psychoses. Most studies have explored substance misuse in psychiatric population and relatively few have focused solely on non-alcohol misuse. Having a clearer differentiation and studying a distinct category of substance misuse allows researchers and healthcare professionals to disentangle correlates and effects of different substances. This study has examined both problematic drug use, and also problematic drug and/or alcohol use among patients with schizophrenia and related psychoses. Given the paucity of related research conducted in Singapore, results from this study can provide valuable insights into drug misuse in the local context and inform healthcare professionals when developing care plans tailored to patients' needs.

DATA AVAILABILITY STATEMENT

Data may be available upon reasonable request and subjected to approval by the institutional review board (IRB). This is a requirement mandated for this research study by our IRB and funders. Requests to access the dataset should be directed to the senior author, Mythily Subramaniam, mythily@imh.com.sg.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Healthcare Group Domain Specific Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AJ, YM, SV, and MS were involved in the design and conception of the study. SC, AJ, JL, SS, ES, and LC were involved in participant recruitment and data collection. SC undertook the data analysis with assistance from JL. SC drafted the manuscript with supervision from AJ and MS. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Long-Acting Injectable Antipsychotic Treatment in Schizophrenia and Co-occurring Substance Use Disorders: A Systematic Review

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Objectives: Co-occurring substance use disorders (SUDs) among individuals with schizophrenia are a prevalent and complex psychiatric comorbidity, which is associated with increased symptom severity, worsened illness trajectory and high rates of treatment non-adherence. Recent evidence suggests that the use of long-acting injectable (LAI) antipsychotics may provide an effective treatment option for individuals with this dual-diagnosis.

Methods: A systematic review of the literature was conducted using the databases PubMed, PsychInfo and Google Scholar for English-language studies, investigating the use of LAIs in co-occurring schizophrenia and substance use disorders (SCZ-SUDs).

Results: Eight reports [one case study (n = 1), one case series (n = 8), three open-label retrospective studies (n = 75), and three randomized controlled trials (n = 273)] investigated the use of LAI antipsychotics in 357 participants with SCZ-SUDs [alcohol use disorder: 5 studies, n = 282; cocaine use disorder: 5 studies, n = 85; amphetamine use disorder: 1 study, n = 1; cannabis use disorder: 3 studies, n = 160; opioid use disorder: 3 studies, n = 19; methylenedioxymethamphetamine (MDMA) use disorder: 2 studies, n = 9; ketamine use disorder: 1 study, n = 4] and were included in this systematic review. Findings indicate significant improvements in substance use related outcomes across 7 of 8 studies, while in 6 of 8 studies, significant improvements in psychopathology-related outcomes were reported.

Conclusions: LAI antipsychotics may be an efficacious intervention option for the treatment of SCZ-SUDs. However, varying methodological rigor, generally small sample sizes and heterogeneity of samples, settings, substances of abuse, tested LAIs and comparators, as well as psychosocial cotreatments and level of reported detail across studies requires that these findings be considered preliminary and interpreted with caution. Further research is required to better understand the effects of LAIs among individuals with SCZ-SUDs.

Keywords: schizophrenia, substance use disorder (SUD), long acting injectable (LAI), antipsychotic, treatment

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INTRODUCTION

Schizophrenia (SCZ) and co-occurring substance use disorders (SUDs) present a prevalent and clinically complex comorbidity (referred to hereafter as SCZ-SUDs) that significantly worsens illness trajectory and is associated with increased morbidity and mortality (1, 2). Approximately 40–65 percent of individuals with schizophrenia also have a co-occurring SUD, with cannabis, alcohol and stimulants representing the most commonly misused substances (2). Persistent misuse of alcohol and drugs by this population is associated with several adverse consequences, including increased rates of homelessness, incarceration, and suicide (2). Moreover, SCZ-SUDs has been linked to increased burden for emergency healthcare services, greater service utilization and higher rates of hospitalization (3). Patients with this dual diagnosis often experience worsened cognitive and negative symptoms, more frequent positive symptoms, higher rates of depression and relapse, and a less stable illness course, than those without such comorbidity (4, 5). Research in this domain points to SUDs as a major barrier to functional recovery among individuals with schizophrenia (4). Additionally, treatment adherence within this population is remarkably low: the SCZ-SUDs comorbidity is associated with reduced therapeutic engagement, as well as high rates of oral medication non-adherence, representing additional barriers to successful treatment and a need for long term solutions (6). The pervasive impact of SCZ-SUDs combined with these complicating factors frame an urgent requirement to develop effective treatment options to improve outcomes for individuals with this comorbidity.

Traditional Treatments for SCZ-SUDs

Psychosocial approaches have been studied for treatment of individuals with SCZ-SUDs, including motivational interviewing and enhancement, relapse prevention training, and cognitive behavioral therapy. A meta-analysis by Bennett et al. (4) found that these psychosocial interventions are associated with moderate efficacy in this population, particularly for improvements in SUD related outcomes such as abstinence or use reductions. However, psychosocial treatments are not recommended as sufficient treatments alone for SCZ-SUDs but should be used in conjunction with pharmacotherapy as a multi-faceted approach to treatment (4).

In terms of medications, there is a scant and inconsistent literature for comorbid SCZ-SUDs. There are two broad (and non-exclusive) psychopharmacological approaches to treatment in this group of patients: (1) the use of antipsychotic medications (e.g., risperidone, clozapine) to improve psychotic symptoms, which may also target mechanisms relevant to SUDs; (2) the use of antipsychotic medications in combination with anti-craving or anti-use agents (e.g., disulfiram, naltrexone). A large-scale systematic review by Azorin et al. (7) evaluated the evidence for oral antipsychotic medication treatment in individuals with SCZ-SUDs from 152 treatment studies. Based on direct and indirect evidence, findings were in support of second-generation (serotonin-dopamine antagonist) rather than first-generation (dopamine antagonist) antipsychotics in this population. Specifically, for individuals with comorbid cocaine use disorder, olanzapine and haloperidol were associated with improvements in both psychiatric and SUD outcomes in several studies (8, 9). For cannabis use disorder, clozapine and ziprasidone were superior, providing improvements in both psychiatric and SUD outcomes (10–12). Finally, olanzapine and quetiapine were most successful in the treatment of SCZ and alcohol use disorder. Regarding SUD-specific medications, results indicate that both naltrexone and disulfiram may be successful in reducing alcohol intake among individuals with schizophrenia and alcohol use disorder (13, 14). Additionally, the tri-cyclic antidepressants imipramine and desipramine were helpful in reducing cocaine craving and use in patients with co-occurring schizophrenia and cocaine use disorder (7). However, authors emphasized that evidence to support these recommendations is limited and should be considered preliminary. There is a critical need for further controlled research in this area, though preliminary indications are promising.

Long-Acting Injectables (LAIs)

A major barrier to successful treatment of SCZ-SUDs remains the low rate of treatment adherence. LAI antipsychotics, one of the most effective psychiatric interventions available for people with schizophrenia, are traditionally used as maintenance therapy in chronic schizophrenia and may be an effective treatment option for SCZ-SUDs while providing a viable solution to improvement of adherence issues in this population (15).

LAI antipsychotics (also known as depot antipsychotics) are injectable formulations of medications that release the active drug slowly (weeks to months, depending on the formulation) (16). Several studies have investigated the efficacy of LAI antipsychotics among individuals with schizophrenia compared to placebo, with positive results: A network meta-analysis by Ostuzzi et al. (17) of 78 RCTs (n = 11,505) indicated that most of the twelve meta-analyzed LAIs outperformed placebo regarding relapse prevention, except for some older first-generation LAIs (i.e., Haloperidol, Bromperidol, Zuclopenthixol and Flupenthazine). For acceptability, most LAIs outperformed placebo, being associated with significantly less all-cause discontinuation (17). In a separate meta-analysis, Kishimoto et al. (18) compared LAI antipsychotics to oral antipsychotics across three different designs; there were 137 studies encompassing 397,319 patients with schizophrenia (i.e., 32 randomized controlled trials (RCTs) [23.4%; n = 8577], 65 cohort studies [47.4%; n = 377,447], and 40 mirror-image studies [29.2%; n = 11,295]). Across all three designs, LAIs were associated with a significantly lower risk of hospitalization or relapse than oral antipsychotics [RCTs: RR = 0.88 (95% CI = 0.79–0.99), p = 0.033; cohort studies: RR = 0.92 (0.88–0.98), p = 0.0044; mirror image studies: RR = 0.44 (0.39–0.51), p < 0.0001]. Across all other outcomes related to effectiveness, efficacy, safety, quality of life, cognitive function, and other outcomes, LAIs were more beneficial than oral antipsychotics in 60 (18.3%) of 328 comparisons, not different in 252 (76.8%) comparisons, and less beneficial in 16 (4.9%) comparisons (mostly driven by unequal antipsychotic type in the LAI and oral antipsychotic group, leading to adverse effect differences).

A separate meta-analysis of tolerability and safety outcomes specifically compared the same LAI and oral antipsychotics in RCTs: LAI formulations demonstrated similar rates of adverse effects in 115 of 119 reported adverse effects, including extrapyramidal symptoms, suggesting they are safe and well tolerated therapeutic options (19).

In addition to superior efficacy and effectiveness with LAIs vs. oral antipsychotics and similar safety and tolerability, including rare cases of neuroleptic malignant syndrome where LAIs cannot be stopped abruptly (20–22) there are a number of potential further benefits to using LAI formulations. Primarily, as LAIs are administered every 2 weeks to 3 or, even, 6 months-depending on medication and formulation (15, 16)-patients experience both a reduced pill burden and are more likely to adhere to treatment (23). Additionally, as LAIs require clinician administration, a more realistic understanding of adherence to treatment is possible, and an enhanced therapeutic alliance can ensue. Individuals taking LAI antipsychotics have also described an improved quality of life compared to those taking oral formulations (15). LAIs have greater bioavailability than oral agents, due to their bypassing liver degradation at first-pass metabolism, allowing for greater available drug concentrations in the central nervous system (23). LAI antipsychotics further have a more reliable delivery system, maintaining steady drug plasma levels and eliminating the peak to trough concentration related side effects common with oral antipsychotics.

In sum, LAI antipsychotics are effective, safe, and tolerable in individuals with schizophrenia, as well as demonstrating considerable potential benefits over oral formulations, notably in terms of adherence. Thus, LAIs may provide a feasible treatment option for individuals with SCZ-SUDs. The current article is a systematic review and critical evaluation of studies investigating the efficacy of LAIs as treatments in SCZ-SUDs.

METHODS

A thorough review of the available literature was conducted by two independent reviewers (A.C. & D.K.) employing the following four databases: PubMed, PsychInfo, Cochrane and Google Scholar. The search strategy followed the Cochrane's PICOS framework for systematic reviews (**P**articipants, **I**ntervention, **C**omparator, **O**utcomes and **S**tudy Design). The following key search terms were used in varying combinations to identify relevant articles: (Schizophreni* OR Schizoaffective OR Psychosis OR psychotic) AND (Substance use OR Substance Dependence OR Substance Use Disorder OR Substance abuse OR Substance Misuse OR Cocaine OR Alcohol OR Amphetamine* OR Opioid* OR opiate* OR Heroin or Cannabi* OR phencyclidine OR ketamine OR psychedelic* OR multisubstance OR polysubstance OR NPS OR "novel psychoactive") AND (Long-Acting Injectable Antipsychotic* OR Long Acting Injectable OR Depot OR Intramuscular OR flupenthixol OR fluphenazine OR Zuclopenthixol OR Haloperidol OR Aripiprazole OR Risperidone OR Paliperidone) AND (Open-Label OR Randomized Controlled Trial OR Retrospective or Observational OR Qualitative OR Prospective).

Articles to be included in this systematic review had to meet the following eligibility criteria:

Inclusion Criteria

- Articles published in peer-reviewed, English-language journals
- The use of both a psychopathology related, and substance use related outcome measure
- Adult participants with schizophrenia-spectrum disorders and co-occurring substance use disorders (alcohol use disorder, cocaine use disorder, cannabis use disorder, amphetamine use disorder, stimulant use disorder, opioid use disorder)
- The use of long-acting injectable antipsychotic treatment as the primary intervention
- All study designs accepted

This systematic review was conducted in accordance with Cochrane's *Preferred Reporting of Systematic Reviews and Meta Analyses* (PRISMA) Guidelines.

RESULTS

Study Selection and Characteristics

The search strategy identified 1,602 articles from the four databases (PubMed, PsychInfo, Cochrane, Google Scholar) and a further 111 articles were identified through other methods (i.e., ClinicalTrials.gov, reference lists of similar review articles, etc.) (see **Figure 1**). After the removal of duplicates, a total of 371 articles remained eligible for abstract review, of which 24 were eligible for full text analysis. Of these 24 articles, 16 were excluded, i.e., 7 due to not including samples with SUDs, three that did not include individuals with schizophrenia-spectrum disorders, and 2 reports each due to being systematic reviews, study protocols, or studies that did not report on SUD outcomes. This left 8 articles meeting complete inclusion criteria that were included for analysis, in alignment with PICOS protocol.

Results Synthesis

Eight reports [one case study ($n = 1$), one case series ($n = 8$), three open-label retrospective studies ($n = 75$), and three randomized controlled trials ($n = 273$)] investigated the use of LAI antipsychotics in 357 participants with schizophrenia and comorbid SUDs [alcohol use disorder: 5 studies, $n = 282$; Cocaine use disorder: 5 studies, $n = 85$; amphetamine use disorder: 1 study, $n = 1$; cannabis use disorder: 3 studies, $n = 160$; opioid use disorder: 3 studies, $n = 19$; methylenedioxymethamphetamine (MDMA) use disorder: 2 studies, $n = 9$; ketamine use disorder: 1 study, $n = 4$] and were included in this systematic review (see **Table 1** for study summaries).

Case Studies and Case Series

A naturalistic case series of eight individuals with schizophrenia and cocaine use disorder treated with haloperidol decanoate or flupenthixol decanoate, was reported by Ouhuha et al. (24). LAI use was not associated with any improvements in either psychotic symptoms or cocaine use. No information on safety and tolerability were reported (24).

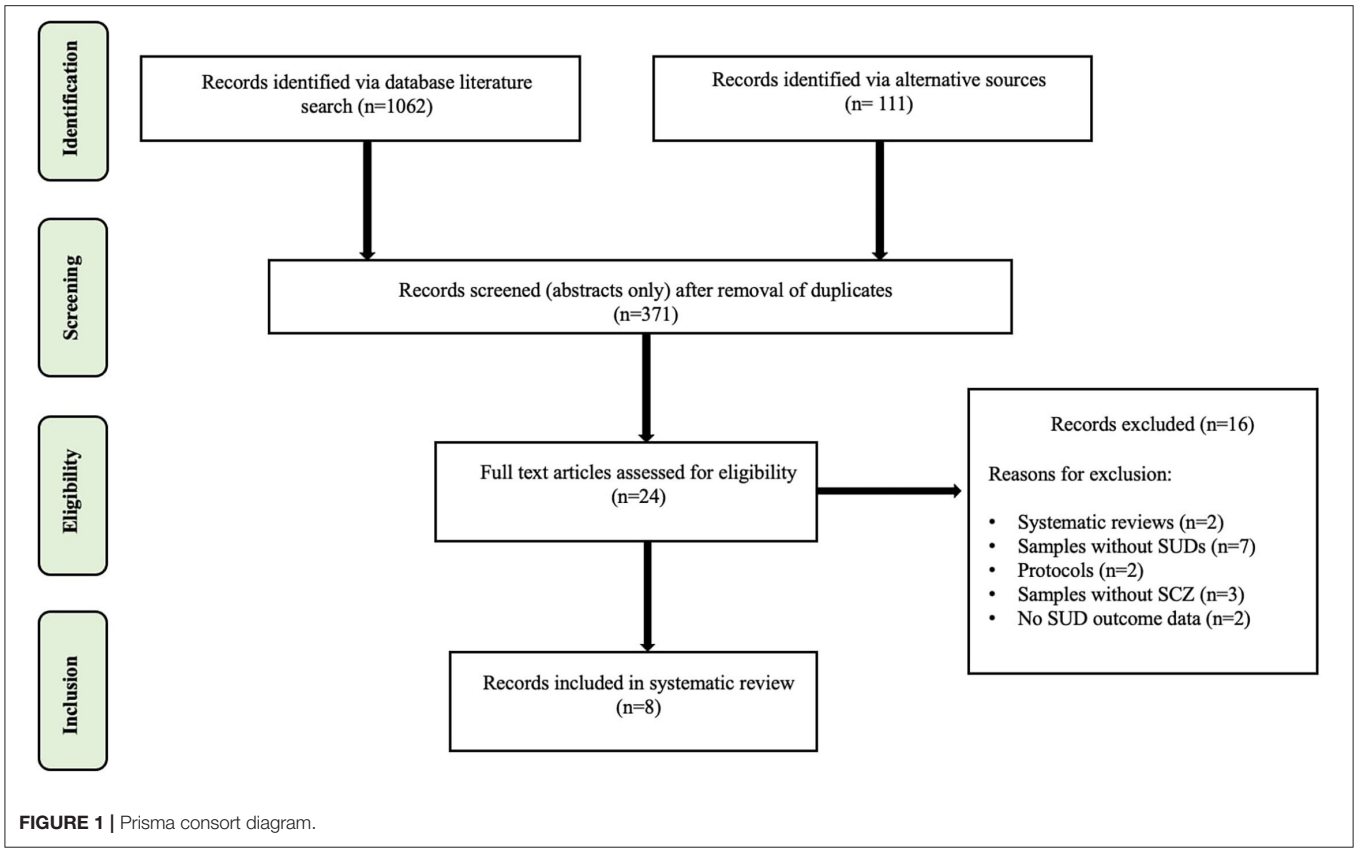

FIGURE 1 | Prisma consort diagram.

A case study by Chen et al. (25) reported a 26-year-old female with schizophrenia and amphetamine use disorder who was treated with 400 mg of LAI-aripiprazole every 2 weeks. This patient reported significant decreases in positive and cognitive symptoms related to schizophrenia, as well as a significant reduction in amphetamine craving. No objective measures of symptom change were included. At 1-year follow up, this participant reported achieving abstinence from amphetamines, which was further confirmed by multiple negative urine toxicology screens. Maintenance of improved psychopathology was also reported at 1-year. No information regarding safety or tolerability of medications were indicated (25).

Non-randomized Studies

Three non-randomized, open-label, retrospective studies ($n = 75$) have been conducted to investigate the use of LAI antipsychotics in SCZ-SUDs. In the first, Levin and colleagues (26) investigated the use of flupenthixol decanoate in eight patients with schizophrenia-spectrum disorders, with a focus on comorbid cocaine use disorder. This study entailed two-phases: participants began the study in a 4-week inpatient phase, followed by a 6-week outpatient phase. Upon study initiation, participants were cross tapered off current antipsychotic medications, and commenced on oral flupenthixol (maximum oral dose of 12 milligrams per day) for a period of 6 days, before being switched to the decanoate version, beginning at 20 milligrams IM /week. All participants were encouraged to attend group psychoeducation and life skills sessions on a weekly basis during the outpatient phase of the trial. Significant reductions in severity of psychopathology were observed across participants at all time points post baseline ($p < 0.05$). Notably, overall changes in cocaine-positive urine screens were not statistically significant, though five of eight participants showed a trending decline in positive urine screens from baseline to follow up. Moreover, participant ratings of cocaine craving were substantially reduced over time, though statistical significance was not reached, probably due to the low statistical power of the study. Study medications were safe and well tolerated by participants (26).

Soyka et al. (27) conducted an open-label relapse prevention trial in 27 people with schizophrenia and comorbid alcohol use disorder. Participants were treated with 10–60 mg of flupenthixol decanoate (mean dose of 30.4 mg) every 2 weeks for a period of 24 weeks. All participants in the intent-to-treat sample consumed at least 120–150 milliliters of pure alcohol daily at baseline. Fourteen participants (66.6%) completed the study, with main reasons for premature termination reportedly due to adverse effects related to study medication (i.e., severe akathisia) or poor adherence with study procedures. At study termination, 8 of 14 participants (57.1%; 38.1% of the total enrolled) were abstinent from alcohol, and an additional two reported significant reductions in use compared to baseline. In participants who did not achieve abstinence, mean drinks per day were reduced from 7.7 (+/- 5.8) to 4.4 (+/- 3.2) ($d = 0.99$). Finally, craving scores, as measured by the *Obsessive-Compulsive*

TABLE 1 | Long acting injectable antipsychotics for comorbid schizophrenia and substance use disorders.

Total studies = 8, Total *N* = 395

Study	Sample	Study design	Intervention	Results	Effect size (Cohen's *d*)
Case studies (*n* = 2 studies, *n* = 9 participants with SSD)					
Ouhuha et al. (24)	*N* = 9 participants with SCZ (*n* = 8) or BP (*n* = 1) and Cocaine use disorder	A naturalistic case series	HPD-IM or FLX-IM (5–15 mg oral equivalents per day)	No significant effects on psychopathology or substance use symptoms were observed.	*
Chen et al. (25)	*N* = 1 participant with SCZ and Amphetamine use disorder	Case study	LAI-AP (400 mg/4 weeks)	Significant reduction in psychotic symptoms and cravings for amphetamines were observed.	*
Open-label trials (*n* = 3 studies, *n* = 75 participants with SSD)					
Levin et al. (26)	*N* = 8 participants with SSD and Cocaine use disorder	A 10-week open-label trial	FLX-IM (40 mg/2 weeks)	A 28 percent reduction in cocaine-positive urine screens, though most patients had a reduction of > 75 percent. Marked reductions in SCZ and depression symptoms were observed across participants.	*
Soyka et al. (27)	*N* = 27 participants with SSD and Alcohol use disorder	An open-label exploratory multicenter 6-month trial	LAI-FLX (10–60 mg)	Significant reductions in alcohol use were observed across participants (8 participants were abstinent at study termination). Minimal improvements in psychopathology were recorded.	Psychopathology outcome: Pre vs. Post-treatment scores LAI-FLX: *d* = 0.35 Substance use outcome: Pre vs. Post-treatment scores LAI-FLX: *d* = 0.99
Szerman et al. (28)	*N* = 40 participants with SSD and one or more SUDs (Alcohol, *n* = 16; Cannabis, *n* = 17; Opioids, *n* = 4; Cocaine, *n* = 9) (# of poly substance users not disclosed)	A multicenter, naturalistic, observational, retrospective study	LAI-AP (*n* = 31, 400 mg/month; *n* =5, 300 mg/month; *n* = 3, 400 mg/3 weeks; *n* = 1, 400 mg/2 weeks)	A 30% reduction in psychotic symptom severity scores were observed across participants. No significant effects on substance dependence severity, apart from cocaine and alcohol. Alcohol use change from 10.6 (3.9) at baseline to 8.9 (3.2) at follow-up. Cocaine use change from 11.2 (4.9) at baseline to 8.4 (3.5) at follow-up.	Psychopathology outcome: Pre vs. Post-treatment scores LAI-AP: *d* = 2.34 Substance use outcome: Pre vs. Post-treatment craving scores Alcohol subgroup: *d* = 0.48 Cocaine subgroup: *d* = 0.66
Randomized controlled trials (*n* = 3 studies, *n* = 273 participants with SSD)					
Rubio et al. (29)	*N* = 115 participant with SCZ and one or more comorbid SUDs (Alcohol, *n* = 101; Cannabis, *n* = 82; Cocaine, *n* = 30; Opioids, *n* = 10; MDMA, *n* = 5) (# of poly substance users not disclosed)	A randomized, controlled, 6-month follow-up study	LAI-RP (n.d.; *n* = 57) or ZP depot (n.d.; *n* = 58)	Participants who received LAI-RP saw significantly greater clean urine screens compared to ZP depot (*P* = 0.005), as well as greater improvements in symptom severity on the PANSS	Psychopathology: Post-treatment scores LAI-RP vs. ZP-depot: *d* = 0.45 Positive urine screens: Post-treatment scores LAI-RP vs. ZP-depot: *d* = 0.52
Green et al. (30)	*N* = 95 participants with SCZ and Alcohol use disorder	A randomized controlled trial	LAI-RP (25 mg titrated to 37.5 mg/2weeks: *n* = 49) or Oral risperidone (4 mg/day; *n* = 46)	No significant SCZ symptom differences between groups. Heavy drinking worsened in the oral risperidone group. LAI-RP saw significantly less heavy drinking days per week compared to oral risperidone (*p* = 0.035).	*

(Continued)

TABLE 1 | Continued

Total studies = 8, Total *N* = 395

Study	Sample	Study design	Intervention	Results	Effect size (Cohen's *d*)
Cuomo et al. (31)	$N = 101$ inpatients with SSD ($n = 63$), FEP ($n = 27$) or BP ($n = 11$) and one or more SUDs (Alcohol, $n = 43$; Cannabis, $n = 61$; Cocaine, $n = 30$; MDMA, $n = 4$; Ketamine, $n = 4$; Opioids, $n = 5$) ($n = 34/101$ were polysubstance users)	A randomized controlled trial	LAI-AP (400 mg/ 4 weeks; $n = 50$) or LAI-PP (100 mg/4 weeks)	Both groups saw significant reductions in clinical symptoms and substance related cravings, as well as improved quality of life. AP, compared to PP, maintained craving and quality of life improvements at 1-year follow up.	Psychopathology: Pre vs. Post-treatment scores LAI-AP: $d = 6.26$ LAI-PP: $d = 4.74$ Craving Intensity: Pre vs. Post-treatment scores LAI-AP: $d = 4.08$ LAI-PP: $d = 1.31$

**Data was insufficient or not available for calculation of effect sizes. LAI, Long-Acting Injectables; SCZ, Schizophrenia; SSD, Schizophrenia Spectrum Disorders; AP, Aripiprazole; FEP, First Episode Psychosis; PP, Paliperidone; BP, Bipolar Disorder; RP, Risperidone; AUD, Alcohol Use Disorder; n.d., No Dose; ZP, Zuclopenthixol; PANSS, Positive and Negative Symptom Scale; FLX, Flupentixol; IM, Intramuscular; HPD, Haloperidol.*

*Drinking Scale (*OCDS) decreased significantly between visit one and two for all participants and remained at this reduced level for the entirety of the study. Regarding changes in psychopathology between baseline and 6 months (post-treatment), 50% of participants were categorized as much improved or very much improved, whilst 21% reported no change or worsened severity of psychopathology at study termination ($d = 0.35$). Nine of 27 participants experienced at least one adverse effect, though study medications were generally well tolerated by participants. Notably, extrapyramidal symptoms were minimal (27).

A recent multicentre, retrospective observational study was conducted by Szerman et al. (28) to determine the efficacy of 400 mg per month of LAI-aripiprazole in forty participants with SCZ-SUDs. Results from this 6-month descriptive study showed that treatment with LAI-aripiprazole was associated with clinically significant reductions in psychopathology severity from baseline–determined by a > 30 percent reduction in scores on the *CGI-S*–for 77.5% of participants ($d = 2.34$). Mean scores on the *WHODAS* (a measure of disability) also decreased significantly ($M = 57.6$, $SD = 8.2$, to M = 42.3, $SD = 4.3$). Substance use changes were most significant in individuals with cocaine use disorder and alcohol use disorder, with 5 of 9 and 3 of 16 participants, respectively, achieving abstinence by the end of the study. All three participants with heroin use disorder were abstinent at 6 months follow-up. Further, scores on the *Severity of Dependence Scale* (SDS) for individuals who did not achieve abstinence within these substance use categories showed significant reductions: cocaine [from $M = 11.2$ (4.9) to $M = 8.4$ (3.5), $d = 0.66$], and alcohol [from $M = 10.6$ (3.9) to $M = 8.9$ (3.2), $d = 0.48$] (all p's < 0.001). Data on safety and tolerability of LAI-aripiprazole was not reported (28).

Randomized Controlled Trials

Three of the included studies were RCTs, encompassing a total of 273 individuals with SCZ-SUDs. In two studies, two LAIs were compared head-to head, and in one RCT an LAI was compared to the same antipsychotic (risperidone), given orally. The earliest of these was conducted by Rubio and colleagues (29) as a 6-month follow up study in 115 participants with schizophrenia and SUDs (alcohol: $n = 101$, cocaine: $n = 30$, cannabis: $n = 82$, opioids: $n = 10$ or MDMA: $n = 5$). Participants were randomized to receive open-label LAI-risperidone (47.2 mg/15 days + 2–6 mg/day of oral risperidone) or zuclopenthixol-depot (200 mg/21 days + 10–50 mg/day of oral zuclopenthixol) over the course of 6 months. Participants also attended weekly substance use training sessions, which were based on the *Substance Abuse Management Model* (SAMM) of Roberts et al. (32). Significant improvements in psychopathology (measured by the Positive and Negative Symptom Scale for Schizophrenia, *PANSS*) were observed in both treatment groups, though LAI-risperidone was superior: 89% of those on risperidone had a reduction of at least 20% on the PANSS (general scale) vs. 50% in the zuclopenthixol-depot group ($d = 0.45$) ($p < 0.001$). Substance use changes were measured as a function of clean urine screens in the weeks following treatment initiation. Individuals in the LAI-risperidone group had a significantly greater number of clean urine screens and a longer time to relapse (first relapse took place in week 9) than the individuals in the LAI-zuclopenthixol group (first relapse took place in week 7) ($d = 0.52$). Additionally, adherence was higher in the LAI-risperidone group, with a greater number of participants also attending the substance use management training sessions, compared to the LAI-zuclopenthixol group. Finally, both LAI-risperidone and LAI-zuclopenthixol were well tolerated by study participants. Notably, there were significantly less extrapyramidal effects observed in the LAI-risperidone group, while antiparkinsonian drugs were used more often in the LAI-zuclopenthixol group, suggesting that LAI-risperidone may be more tolerable in this population (29).

A second randomized trial, by Green et al. (30) compared the efficacy of LAI vs. oral risperidone in 95 participants with schizophrenia and co-occurring alcohol use disorders over a 6-month period. Participants were titrated to a mean dose of 4.3 mg per day in the oral risperidone group, or a mean dose of 32.7 mg every 2 weeks in the LAI-risperidone group. Explanatory analyses indicated that heavy drinking significantly worsened in the oral group over the study period (average increase of 0.68 heavy drinking days per week), though not in the LAI-risperidone group (average decrease in heavy drinking days−0.011) ($p = 0.24$). No differences between groups were observed in drinking intensity (days of drinking per week). Additionally, no differences

in symptom severity (measured by the PANSS) were found post-treatment in either group. Treatment adherence was significantly lower in the oral risperidone group compared to the LAI group. Finally, safety, tolerability and side effect profiles were similar for both the oral and LAI-risperidone groups, with a total of 79% of all participants experiencing an adverse event during the study (30).

Finally, Cuomo et al. (31) conducted a comparison of two LAI antipsychotic medications in 125 inpatient participants with a diagnosis of either schizophrenia or bipolar disorder (with psychotic features) and a comorbid SUD (alcohol: $n = 43$, cannabis: $n = 61$, cocaine: $n = 30$, MDMA: $n = 4$, opioids: $n = 5$ and ketamine: $n = 4$). Participants were randomized to receive either 400 mg of intramuscular aripiprazole monohydrate or 100 mg intramuscular paliperidone palmitate once per month, for a period of 12 months. Significant improvements across measured outcomes from baseline to follow up (1-year) were observed for both groups. Specifically, LAI-aripiprazole and LAI-paliperidone were both associated with improved symptom severity (based on *Clinical Global Impressions Scale, CGI*) with large effect sizes of $d = 6.26$ and $d = 4.74$, respectively (p's <0.001). Further, LAI-aripiprazole was superior to LAI-paliperidone in the reduction of substance-related craving intensity, though both groups showed significant improvements in this domain ($d = 4.48$ and $d = 1.31$, respectively) (p-value < 0.001). Notably, two participants in the LAI-paliperidone group reported increased craving post-treatment. This result is of particular interest, as baseline values indicated stronger craving intensity in participants allocated to the LAI-aripiprazole group. Additionally, both medications had significant improvements in quality of life, though effect sizes for LAI-aripiprazole were much larger than those for LAI-paliperidone ($d = 1.98$ and $d = 0.65$, respectively) (p-value < 0.001). Few side effects were reported, of which none led to study discontinuation. Side effects were less in the LAI-aripiprazole group compared to the LAI-paliperidone group, demonstrating similar side effect profiles and tolerability as their oral formulations. Five patients in the LAI-paliperidone group did develop hyperprolactinemia, of whom four also developed galactorrhea. Finally, two participants in the LAI-aripiprazole group developed akathisia, leading to a reduction of dose from 400 to 300 mg, which eliminated the side effect in both participants. Study related changes in weight were not reported (31).

DISCUSSION

The current article is a systematic review of available studies (case reports, case series, open-label studies, and randomized controlled trials) assessing the efficacy of LAI antipsychotics for the treatment of schizophrenia and co-occurring SUDs.

A single case report (25) observed a positive outcome for LAI-aripiprazole treatment in a woman with schizophrenia and co-occurring amphetamine use disorder, while a small-scale case series showed no benefit for LAI-flupenthixol or LAI-haloperidol in comorbid schizophrenia and cocaine use (24). While instructive, case series and case reports are inevitably subject to reporting bias, and thus, little can be concluded from these studies.

The three open-label studies reported in this review (26–28) are aligned in terms of apparent efficacy of LAIs for psychotic symptoms and indices of substance use (specifically, alcohol and cocaine). However, all studies involved small samples, were of retrospective design and were limited in duration. Moreover, the different psychotropic agents could not be compared with one another. Alone, these studies do not allow any firm conclusions to be drawn regarding the efficacy of the LAIs themselves (i.e., over, and above simple inclusion in the study).

The three randomized controlled trials included in this review (29–31) allow for the comparison of either LAI vs. oral antipsychotics or the comparison across different LAIs. Green et al. (30) found that LAI-risperidone was associated with better alcohol-related outcomes on some indices, compared to oral risperidone. This study lends support to the use of LAIs in people with schizophrenia who also have alcohol use disorder and underscore the benefits of assured adherence in this population.

The study by Rubio et al. (29) compared a first-generation antipsychotic, LAI-zuclopenthixol, with a second-generation agent, LAI-risperidone. It is of note that outcomes with LAI-risperidone were somewhat superior, as it has been suggested that the second-generation antipsychotic LAIs have improved tolerability compared to the older agents (33). Further, the review by Azorin et al. (7) suggested that some of the second-generation antipsychotics may have advantages over the older, first-generation medications in terms of efficacy for people with schizophrenia and a comorbid SUD. In terms of a comparison between LAI antipsychotic agents (i.e., aripiprazole monohydrate and paliperidone palmitate), Cuomo and colleagues (31) observed similar efficacy of both agents in the treatment of psychotic symptoms, though aripiprazole had stronger anti-craving effects in SCZ-SUDs.

Notably, none of the reviewed randomized controlled trials included a placebo condition. Though this can be defended based on clear evidence for the efficacy of antipsychotics (and LAIs in particular) in reducing the risk of relapse in people with schizophrenia (17), the absence of placebo-controlled studies limits the interpretation of results.

In general, all study medications in LAI form were considered safe and well tolerated by study participants. This aligns with previous research that has demonstrated similar side effect profiles and risk of adverse events and extrapyramidal symptoms for both LAI and oral formulations of antipsychotic medications (15, 19).

Strengths and Limitations

This systematic review was conducted in accordance with internationally accepted guidelines for systematic reviews (PRISMA and PICOS guidelines) and contains a broad range of all available literature on the use of LAIs in SCZ-SUDs.

There are some limitations to the current review, as well as methodological limitations of reviewed studies, which must be highlighted. A wide range of study designs were deliberately included, given the paucity of trials in the area. Despite this broad set of inclusion criteria, our yield was modest, and the studies were highly heterogeneous, precluding a meta-analysis.

Regarding methodological limitations, the reviewed studies employed a variety of LAI medications at different doses and at

varying dose intervals (as determined by the particular product), making comparisons across studies problematic. Also, a wide variety of different substances of abuse were included, with many of the larger studies including participants who simultaneously abused a number of substances: alcohol, cannabis, opioids, cocaine and MDMA in the study of Rubio et al. (29) and those agents in addition to ketamine in the study of Cuomo et al. (31). Of the RCTs, only that of Green et al. (30) included people using only one substance (i.e., alcohol). It is thus difficult to draw conclusions about LAI efficacy in patients with specific drugs of abuse.

The types of participants included in the reviewed studies were generally later in their illness course, which emphasizes the gap in understanding the early use of LAI antipsychotics in people with emerging psychosis and SUDs. This is a pertinent problem, given the various guidelines, which call for judicious use of LAIs earlier in illness course (i.e., first episode psychosis) [e.g., (34, 35)]; and compelling data for their efficacy in such individuals, including from the recent PRELAPSE study (36).

Length of follow-up also varied significantly, ranging from a few weeks to 12 months. Arguably, the proof of efficacy and safety of LAIs is determined via maintenance of effects in the years of follow-up. Thus, only the randomized trial conducted by Cuomo et al. (31) is of sufficient length for meaningful clinical conclusions to be drawn about longer-term use, and longer-term trials are of critical need.

Most sample sizes were small and did not have sufficient statistical power to allow analyses of sub-groups, a notable issue due to the heterogeneity of substances of abuse included (see above). The study settings also varied, ranging from inpatient to community environments, or a combination of the two. Finally, concomitant psychosocial interventions also varied across studies, ranging from none (or not specified) to adjunct use of an established efficacious psychosocial intervention for SUDs (29).

CONCLUSIONS

Substance use disorders are common among people with schizophrenia and have been shown to worsen the longitudinal course of illness, reduce medication adherence and increase rates of relapse. The fact that a number of LAI second generation antipsychotics show efficacy and good tolerability for people with schizophrenia and are associated with enhanced adherence and reduced relapse rates, suggests they deserve special consideration in people with SCZ-SUDs. The evidence reviewed here supports this assertion, but the paucity of studies and methodological shortcomings temper this conclusion. The sparsity of available literature on the subject speaks to the difficulties in conducting research in populations with comorbid substance use problems, who are often specifically excluded from clinical trials. Given the prevalence of comorbid substance use in individuals with severe mental illness, further research in this area is urgently required.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

AC and DK performed literature review. AC wrote first draft of the manuscript. AC and DC wrote sections of the manuscript. All authors contributed to the revision and approval of the submitted manuscript.

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Features of Psychotic Symptoms in Methamphetamine Use Disorder Patients and Ketamine Use Disorder Patients: A Cross-Sectional Study

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Background: Methamphetamine and ketamine are commonly used club drugs. Both of them have been reported to mimic psychotic symptoms of schizophrenia. However, the prevalence and detailed features of psychotic symptoms among methamphetamine use disorder (MUD) and ketamine use disorder (KUD) patients are largely unknown. This study aimed to measure psychotic symptoms among patients with MUD and KUD.

Methods: A total sample of 842 patients from voluntary drug rehabilitation centers, including 462 MUD patients and 380 KUD patients, were invited to this study. The Positive and Negative Syndrome Scale (PANSS) was applied to assess psychotic symptoms in these two groups of patients.

Results: The prevalence of psychotic symptoms was significantly higher among MUD patients than KUD patients (75.1 vs. 50.5%, 95% CI: 3.532 – 11.858, $p < 0.001$). Compared with KUD patients, MUD patients were more likely to experience positive symptoms (PANSS positive scores: 11.5 ± 6.07 vs. 15.1 ± 8.22, $P < 0.001$) and negative symptoms (PANSS negative scores: 12.4 ± 6.60 vs. 14.5 ± 8.63, $P < 0.001$), but not general symptoms (PANSS general scores: 31.2 ± 13.90 vs. 32.2 ± 15.13, $P < 0.001$).

Conclusions: The current study found that more than half of MUD and KUD patients experienced psychotic symptoms, and that patients with MUD are more likely to experience positive and negative symptoms than patients with KUD. The findings provide a new perspective for exploring the neuropathological mechanism of psychotic symptoms of schizophrenia.

Keywords: methamphetamine use disorder, ketamine use disorder, psychotic symptoms, positive symptoms, negative symptoms, schizophrenia

INTRODUCTION

The use of synthetic drugs such as methamphetamine and ketamine has been recognized as an increasingly serious and important public health issue in China and other countries (1–3). A series of studies indicate that chronic use of both methamphetamine and ketamine can lead to psychotic symptoms (4–6), which are mainly manifested as persistent hallucinations, delusions, and negative symptoms.

The experience of psychotic symptoms ranged from 26 to 46% among people with methamphetamine use disorder (MUD) (7). A study with 292 MUD patients from a drug rehabilitation center in Malaysia showed that 47.9% of them had a history of psychotic symptoms (8). Studies show that patients with ketamine use disorder (KUD) have a relatively lower risk of psychotic symptoms than those of MUD patients, around 8% (9). In drug-free healthy individuals, low-dose administration of either ketamine or amphetamine produced positive symptoms (such as conceptual disorganization) and euphoria. Ketamine mainly produced perceptual changes, concrete ideation, and unusual mannerisms, negative symptoms, and disrupted delayed recall. Amphetamine mainly produced hostility, grandiosity, and somatic concern. The findings from the above study indicate that glutamate and DA may differentially contribute to psychosis (10). A recent systematic review and meta-analysis further confirmed that ketamine induced psychosis-like symptoms in healthy volunteers (11).

The neuropathological mechanisms of psychotic symptoms are not fully understood. Both methamphetamine and ketamine use-induced psychotic symptoms can mimic symptoms of schizophrenia. Methamphetamine has been used for the study of the dopamine (DA) model of schizophrenia (12). Ketamine, as an N-methyl-D-aspartate (NMDA) antagonist, has often been studied for the glutamate model of schizophrenia (13). DA plays a well-recognized role in a variety of neurophysiologic functions such as cognition, mood and reward (14). Methamphetamine dysregulates both DA transmission and DA reuptake, and it mainly acts on DA transporter (DAT) and the vesicular monoamine transporter 2 (VMAT2) to inhibit the reabsorption of DA and promote the release of DA in the Nucleus Accumbens (NA) *via* the sigma receptor (15). Ketamine primarily impairs NMDA glutamate receptor neurotransmission, and it has been suggested to increase cortical glutamate release via indirect inhibition of GABAergic interneurons, implicating in the pathophysiology of schizophrenia (16).

Although a line of study has shown that the psychotic symptoms caused by methamphetamine and ketamine are similar to those of schizophrenia. The prevalence and detailed features of psychotic symptoms (including positive, negative and general symptoms) among methamphetamine use disorder (MUD) and ketamine use disorder (KUD) patients are largely unknown. The aim of this study was to measure psychotic symptoms among patients with MUD and KUD. Based on previous studies, this study assumed that the prevalence of positive and negative symptoms would be higher among MUD patients than KUD patients. The findings from this study may provide a preliminary basis for clinical interventions of MUD and KUD associated psychosis, and give a new perspective for exploring the neuropathological mechanism of psychotic symptoms of schizophrenia.

METHODS

Recruitment

This cross-sectional study assessed the prevalence of psychotic symptoms in a clinic-based sample of KUD patients and MUD patients. We recruited 380 KUD patients and 462 MUD patients from two rehabilitation centers in mainland China (Guangzhou Baiyun Voluntary Drug Rehabilitation Center in Guangdong Province and Kangda Voluntary Drug Rehabilitation Center in Hunan Province) from January 2012 to October 2016. Drug use (methamphetamine or ketamine) was validated via urine toxicology screen and self-report data. All participants were diagnosed through a semi-structured interview (Structured Clinical Interview for DSM-IV-TR, Axis I, Patient Version, SCID-I/P) by experienced psychiatrists (with more than 5 years of clinical experience). The Positive and Negative Syndrome Scale (PANSS) was used to assess psychotic symptoms in these two groups of patients. Before enrolling patients into this study, all psychiatrists who involved in current study were trained to administer the PANSS and SCID-I/P with good reliability (>0.80). The inclusion criteria were: inpatients from drug rehabilitation center; after detoxification and had 2 weeks of drug abstinence; met diagnosis for MUD or KUD; used methamphetamine or ketamine for more than 12 months; 18 years of age or older; willing to participant, being able to communicate in Chinese. The exclusion criteria were: suffering from other severe mental and/or physical illnesses; have a history of brain trauma; and have other substance use disorders (except for nicotine).

Ethics

Informed consent was obtained from all patients in the study. The procedures were performed in accordance with the Declaration of Helsinki. The ethical approval for this study was obtained from the Ethics Committee of the Second Xiangya Hospital, Central South University (No. S163, 2011).

Measures

Sociodemographic and Drug Use Information

Sociodemographic and drug use information, such as age, gender, education, age of the first use, quantity of drug (g) per time, drug craving, and times of rehabilitation were collected by self-reported questionnaires. Methamphetamine or ketamine craving was assessed by the Visual Analog Scale for Craving (VASc) (17). The VASc displays a scale from 0 (left, no craving) to 10 (right, most extreme craving).

The Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (18) is a 30-item scale designed to obtain a measure of positive (items P1 to P7) and negative (items N1 to N7) symptoms in schizophrenic patients, as well as a measure of general psychopathology (items G1 to G16). All 30 items are rated on a 7-point scale: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate–severe, 6 = severe, 7 = extreme. Factorial analyses of subscales found that a five-factor model better captures PANSS structure in schizophrenia samples (19). In the five-factor model, smaller groupings of items represent the following symptoms: positive (items P1, P3, P5, G9), negative (items N1, N2, N3, N4, N6, G7), disorganized/concrete (items P2, N5, G11), excited (items P4, P7, G8, G14), and depressed (items G2, G3, G6) symptoms.

Statistical Analyses

Statistical analysis was performed using the SPSS for Windows (Version 23, SPSS Inc., Chicago, IL, USA) software package. Descriptive statistics were used to examine demographic, drug use, and psychotic characteristics. Independent sample *t*-tests or χ^2-square tests were performed to determine group differences in demographic characteristics, substance use profiles, and psychotic symptoms between these two groups. Multiple linear regression models have been applied to evaluate the impact of types of used drugs (methamphetamine or ketamine), gender, age, age of first-time drug use, duration of drug use (months), and frequency during the last drug use month on psychotic symptoms (PANSS total score). An alpha level of 0.01 was set to determine statistical significance.

RESULTS

Sociodemographic and Drug Use Characteristics

This study included 842 drug users (462 MUD patients and 380 KUD patients). Demographic and drug use characteristics of patients with MUD and KUD are shown in **Table 1**.

TABLE 1 | Sample characteristics.

	MUD patients (n = 462)	KUD patients (n = 380)	t/χ^2	p
Demographic variables				
Age, years	29.4 ± 6.32	26.8 ± 5.36	6.39	<0.001
Range, years	14–53	16–52		
Female	28 (6.1%)	43 (11.3%)	−7.46	0.006
Education level, years,	11.2 ± 2.78	11.6 ± 2.50	−2.58	0.010
Unmarried	224 (48.5%)	224 (58.9%)	−9.17	0.002
Unemployed	98 (21.2%)	78 (20.5%)	0.06	0.808
Body mass index	23.3 ± 3.56	21.8 ± 4.20	5.68	<0.001
Drug use variables				
Age of the first use	25.5 ± 6.45	21.9 ± 5.29	8.88	<0.001
Duration, months,	43.1 ± 30.12	57.5 ± 32.31	−6.63	<0.001
Range, months,	2–204	1–157		
Times of drug use per day during the last 12 months	2.4 ± 1.08	1.8 ± 1.06	7.54	<0.001
Times of drug use per day during the last 3 months	2.4 ± 1.20	1.7 ± 1.07	9.03	<0.001
Quantity of drug (g) per time	0.6 ± 0.79	1.2 ± 1.28	−9.13	<0.001
Craving by VASc	3.5 ± 2.78	5.3 ± 2.80	−9.01	<0.001
Times of rehabilitation	1.4 ± 1.65	1.6 ± 2.34	−1.88	0.060
Cigarette smoking	444 (96.1%)	367 (96.6%)	−0.11	0.716
Cigarettes per day	19.8 ± 10.72	18.7 ± 8.17	1.68	0.094
Duration, years	11.7 ± 5.68	9.4 ± 5.10	5.59	<0.001
Alcohol drinking	137 (29.7%)	133 (35.0%)	−2.74	0.098
Duration (years)	10.0 ± 6.12	8.2 ± 5.14	2.39	0.018
Other drugs use[a]				
Methamphetamine	—	123 (32.4%)		
Ketamine	55 (11.9%)	—		
Ma Gu (amphetamine+caffeine)	166 (35.9%)	70 (18.4%)		
Ecstasy	40 (8.7%)	61 (16.1%)		
Marijuana	11 (2.4%)	20 (5.3%)		
"Happy Water"[b]	5 (1.1%)	21 (5.5%)		
Heroin	17 (3.7%)	3 (0.8%)		
Diazepam	0 (0.0%)	7 (1.8%)		
Dolantin	0 (0.0%)	1 (0.3%)		
Tramadol	2 (0.4%)	0 (0.0%)		
Psychotic symptoms	347 (75.1%)	192 (50.5%)	54.69	<0.001
Onset age	28.5 ± 6.32	25.4 ± 5.49	6.05	<0.001
Duration (month)	15.1 ± 19.43	3.5 ± 24.53	4.01	<0.001
PANSS total score	61.8 ± 29.43	55.3 ± 24.57	3.48	0.001

Data are in mean ± SD or n (%).
MUD, methamphetamine use disorder; KUD, ketamine use disorder; VASc, the visual analog scale for craving.
Significantly different from control group, $p < 0.01$.
[a] *MUD patients only had methamphetamine dependence, KUD patients only had ketamine dependence (except for nicotine). However, each person could have tried other drugs for one or more than one times.*
[b] *"Happy Water (Kai Xin Shui)" is a kind of mixed liquid containing club drugs such as methamphetamine, amphetamine, ketamine, ecstasy.*

Factors Predicting Psychotic Symptoms

Multiple linear regression models were applied to evaluate the predictors (demographic and drug use factors) for psychotic symptoms (PANSS total score). As shown in **Table 2**, only types of used drugs (methamphetamine or ketamine) were associated with PANSS total score, indicating that MUD patients experienced more psychotic symptoms than KUD patients did ($p < 0.001$).

Psychotic Symptoms in MUD Patients and KUD Patients

A total of 75.1% (n = 347) MUD patients and 50.5% (n = 192) KUD patients experienced psychotic symptoms (**Table 1**). Compared with KUD patients, MUD patients were more likely to suffer from psychotic symptoms (95% CI: 3.532–11.858, $p < 0.001$). The scores of PANSS were compared between these two groups. We find that compared with KUD patients, MUD patients were more likely to experience positive symptoms (11.5 ± 6.07 vs. 15.1 ± 8.22, $P < 0.001$) and negative symptoms (12.4 ± 6.60 vs. 14.5 ± 8.63, $P < 0.001$), but not general symptoms (31.2 ± 13.90 vs. 32.2 ± 15.13, P = 0.331) (**Table 3**). The proportion of each symptom in both

TABLE 2 | MLR model predicting increase in PANSS total score.

Variable	B	Beta	*t*	95% Confidence interval	*p*
Types of used drugs (methamphetamine or ketamine)	7.695	0.140	3.628	3.532 to 11.858	<0.001
Gender	6.475	0.066	1.883	−0.275 to 13.224	0.060
Age	0.603	0.133	1.139	−0.436 to 1.641	0.255
Age of first-time drug use	−0.720	−0.163	−1.391	−1.736 to 0.296	0.165
Duration of drug use (M)	0.010	0.012	0.201	−0.089 to 0.110	0.841
Frequency during the last drug use month	0.470	0.020	0.564	−1.166 to 2.106	0.573

Multiple linear regression model (MLR) model.
Y = 38.422 + (7.695) types of used drugs + (6.475) gender + (0.603) age – (0.720) age of first-time drug use + (0.010) duration of drug use (Months) + (0.470) frequency during the last drug use month.

TABLE 3 | Positive, negative, and general symptoms assessed by PANSS between two groups.

	MUD patients (*n* = 462)	KUD patients (*n* = 380)	t/x^2	*p*
Positive	15.1 ± 8.22	11.5 ± 6.07	7.11	<0.001
p1 (Delusions)	281 (47.2%)	102 (26.8%)		
p2 (Conceptual)	223 (48.3%)	130 (34.2%)		
p3 (Hallucinations disorganization)	162 (35.1%)	122 (32.1%)		
p4 (Excitement)	256 (55.4%)	194 (51.1%)		
p5 (Grandiosity)	187 (40.5%)	110 (28.9%)		
p6 (Suspiciousness/Persecute)	242 (52.4%)	107 (28.2%)		
p7 (Hostility ion)	230 (49.8%)	114 (30.0%)		
Negative	14.5 ± 8.63	12.4 ± 6.60	3.78	<0.001
N1 (Blunted affect)	230 (49.8%)	192 (50.5%)		
N2 (Emotional withdrawal)	241 (52.2%)	191 (50.3%)		
N3 (Poor rapport)	226 (48.9%)	164 (43.2%)		
N4 (Passive/Apathetic social)	242 (52.4%)	200 (52.6%)		
N5 (Difficulty in abstraction withdrawal)	187 (40.5%)	115 (30.3%)		
N6 (Lack of spontaneity)	197 (42.6%)	151 (39.7%)		
N7 (Stereotyped thinking)	163 (35.3%)	106 (27.9%)		
General	32.2 ± 15.13	31.2 ± 13.90	0.97	0.331
G1 (Somatic concern)	253 (54.8%)	271 (71.3%)		
G2 (Anxiety)	304 (65.8%)	300 (78.9%)		
G3 (Guilt feelings)	256 (55.4%)	244 (64.2%)		
G4 (Tension)	257 (55.6%)	200 (52.6%)		
G5 (Mannerisms)	154 (33.3%)	94 (24.7%)		
G6 (Depression posturing)	235 (50.9%)	209 (55.0%)		
G7 (Motor retardation)	167 (36.1%)	145 (38.2%)		
G8 (Uncooperativeness)	161 (34.8%)	97 (25.5%)		
G9 (Unusual thought)	199 (43.1%)	105 (27.6%)		
G10 (Disorientation content)	37 (8.0%)	72 (18.9%)		
G11 (Poor attention)	203 (43.9%)	171 (45.0%)		
G12 (Lack of judgment and symptom)	240 (51.9%)	137 (36.1%)		
G13 (Disturbance of volition insight)	218 (47.2%)	210 (55.3%)		
G14 (Poor impulse control)	257 (55.6%)	208 (54.7%)		
G15 (Preoccupation)	184 (39.8%)	88 (23.2%)		
G16 (Active social avoidance)	225 (48.7%)	187 (49.2%)		

Data are in mean ± SD or n (%).
PANSS, the positive and negative syndrome scale.
Percentage of each symptom assessed by PANSS with ≥ 2 points (from minimal to extreme).

groups, including each item of the PANSS positive, negative, and general symptoms, are also shown in **Table 3**. A five-factor model of positive, negative, disorganized/concrete, excited, and depressed symptoms was also compared between two groups (**Table 4**).

DISCUSSION

Principal Findings

The current study assessed the prevalence and detailed features of psychotic symptoms among MUD and KUD patients. This study found that 75.1% MUD patients and 50.5% KUD patients from drug rehabilitation centers in China experienced psychotic symptoms, indicating that MUD patients are more likely to suffer from psychotic symptoms (including positive and negative symptoms) than KUD patients. However, MUD patients and KUD patients showed no group differences in overall general symptoms.

Psychotic Symptoms in MUD Patients and KUD Patients

Compared with previous studies, our study found relatively high prevalence of psychotic symptoms in MUD patients and KUD patients, especially in MUD patients. One study reported that the prevalence of psychotic symptoms ranged from 26 to 46% in MUD patients (7). Another study reported that 47.9% MUD patients had history of psychotic symptoms (8). A study found that only 8% KUD had psychotic symptoms (9). However, our study found more than half of KUD patients and two-thirds of MUD patients experienced psychotic symptoms.

This study found that, compared with KUD patients, MUA patients were more likely to experience both positive and negative symptoms, but not general symptoms. Previous studies suggest that methamphetamine mainly causes psychotic symptoms by causing DA system dysfunction, acting on DA transmission in the central nervous system via the inhibition of the DA transporter and the VMAT2, and leading to the increase of DA concentration in the mesolimbic, nigrostriatum, and mesocortical, resulting in psychotic symptoms, mainly positive symptoms (6, 20). Furthermore, in the nigrostriatum, dysregulated DA neuron firing can abnormally highlight irrelevant stimuli, thereby producing percepts and thoughts with aberrant salience, resulting to delusions and hallucinations (10, 21). In terms of methamphetamine use induced negative symptoms, one possible explanation is that the reduction of the signal-to-noise ratio of adaptive phasic signaling has the potentiality to reduce the

TABLE 4 | PANSS scores by the five-factor model between two groups.

PANSS scores and items	MUD patients	KUD patients	*t*	*p*
	Mean ± SD	Mean ± SD		
The five-factor model				
A. Positive factor	8.2 ± 4.83	6.4 ± 3.73	6.01	<0.001
B. Negative factor	12.7 ± 7.64	11.2 ± 6.06	3.04	0.002
C. Disorganized/ concrete (cognitive) factor	5.7 ± 3.09	5.1 ± 2.62	3.06	0.002
D. Excited factor	8.35 ± 4.27	7.2 ± 3.57	4.37	<0.001
E. Depressed factor	7.1 ± 3.83	7.4 ± 3.83	−1.08	0.282

PANSS, the positive and negative syndrome scale; MUD, methamphetamine use disorder; KUD, ketamine use disorder.

appetitive properties of a given reward, thereby leading to motivation and anhedonia, and other negative symptoms.

Research indicates that ketamine produces psychotic symptoms through dysfunction in the glutamate system. As a high affinity non-competitive antagonist of NMDAR, ketamine has been shown to mimic more negative symptoms than active symptoms of psychotic behavior in previous studies (10, 21). A line of study found that ketamine can produce positive and negative symptoms similar to schizophrenia with long-term use (22, 23), which is consistent with our results. A preclinical study found that ketamine causes psychotic episodes by significantly increasing synaptic glutamate release in the cortex and striatum (24).

High prevalence of psychosis among MUD patients and KUD patients in current study indicates that both the glutamate and DA systems directly or indirectly interact with psychotic symptoms (4, 10, 13). The psychotic symptoms were more easily induced by MA than ketamine, indicating that the dysfunction of the glutamate system may cause psychotic symptoms through indirect (not direct) action on the DA system. Methamphetamine or amphetamine induced hyper-dopaminergic states would be associated with the more vulnerability of psychosis (25). Previous studies proved that modulation of the DA system affects cortical glutamate levels (mainly in the prefrontal lobe) and local glutamate release; glutamate levels can affect DA release in the striatum; and the administration of ketamine can lead to the increase of DA release in the striatum. Low glutamate release or insufficient activation of NMDA receptors on cortical GABA interneurons may lead to hyperactive striatal dopaminergic activity (13, 26–28). Clinically, the use of DA receptor antagonists for ketamine-induced psychosis further provides evidence of the interaction of glutamate and DA (29). Thus, we speculate that the glutamate system can use a common pathway that interacts with the DA system to contribute to the occurrence of psychotic symptoms.

In short, comparing psychotic symptoms induced by the nonmedical use of ketamine and methamphetamine, we have demonstrated that some features of psychotic symptoms in MUD and KUD patients are highly similar to schizophrenia. Our study indicates the significance of identifying and treating psychotic symptoms in MUD and KUD patients, and provides a preliminary basis for clinical identification of the characteristic of psychotic symptoms between schizophrenia and substance use disorder.

LIMITATIONS

This study has some limitations that need to be considered. First of all, we only assessed residual psychotic symptoms but not acute effects of methamphetamine and ketamine. All participants were from voluntary drug rehabilitation centers, and they were not randomly sampled, so the representativeness is limited. Secondly, most patients in the present study were male, so we did not assess gender differences for psychotic symptoms. Thirdly, some drug use variables were different between MUD patients and KUD patients. Compared with MUD patients, KUD patients showed an earlier age of the first use, longer duration of ketamine use, higher quantity of drug use per time, and higher drug craving level. However, this study found more MUD patients experienced psychotic symptoms than KUD patients. The underlying mechanism needs to be further researched. Lastly, some MUD or KUD patients also used other drugs. However, this study excluded patients with other substance use disorders (excluding nicotine).

CONCLUSION

In conclusion, this study found that psychotic symptoms are commonly reported by MUD patients and KUD patients from drug rehabilitation centers, and that MUD patients are more likely to suffer from psychotic symptoms (but not general symptoms) than KUD patients. These findings indicate the importance of assessing psychotic symptoms among these two groups of patients. It also provides a new perspective for exploring glutamatergic model and dopaminergic model of psychosis.

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 protocol has been approved by Ethics Committee of the Second Xiangya Hospital, Central South University (No. S163, 2011). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL conceived the study and took the lead in writing the manuscript. YL and MX did the literature review. TL did the statistical analyses. YL, TL, and MX drafted the report. YL,

CQ, and QW collected the data. TL, MX, and JT interpreted the data and commented on the manuscript. JT supervised the study. All authors contributed to the article and approved the submitted version.

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Evidence for Schizophrenia-Specific Pathophysiology of Nicotine Dependence

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Tobacco use is the top preventable cause of early mortality in schizophrenia. Over 60% of people with schizophrenia smoke, three times the general prevalence. The biological basis of this increased risk is not understood, and existing interventions do not target schizophrenia-specific pathology. We therefore used a connectome-wide analysis to identify schizophrenia-specific circuits of nicotine addiction. We reanalyzed data from two studies: In Cohort 1, 35 smokers (18 schizophrenia, 17 control) underwent resting-state fMRI and clinical characterization. A multivariate pattern analysis of whole-connectome data was used to identify the strongest links between cigarette use and functional connectivity. In Cohort 2, 12 schizophrenia participants and 12 controls were enrolled in a randomized, controlled crossover study of nicotine patch with resting-state fMRI. We correlated change in network functional connectivity with nicotine dose. In Cohort 1, the strongest ($p < 0.001$) correlate between connectivity and cigarette use was driven by individual variation in default mode network (DMN) topography. In individuals with greater daily cigarette consumption, we observed a pathological expansion of the DMN territory into the identified parieto-occipital region, while in individuals with lower daily cigarette consumption, this region was external to the DMN. This effect was entirely driven by schizophrenia participants. Given the relationship between DMN topography and nicotine use we observed in Cohort 1, we sought to directly test the impact of nicotine on this network using an independent second cohort. In Cohort 2, nicotine reduced DMN connectivity in a dose-dependent manner ($R = -0.50$; 95% CI -0.75 to -0.12, $p < 0.05$). In the placebo condition, schizophrenia subjects had hyperconnectivity compared to controls ($p < 0.05$). Nicotine administration normalized DMN hyperconnectivity in schizophrenia. We here provide direct evidence that the biological basis of nicotine dependence is different in schizophrenia and in non-schizophrenia populations. Our results suggest the high prevalence of nicotine use in schizophrenia may be an attempt to correct a network deficit known to interfere with cognition.

Keywords: schizophrenia, nicotine dependence, resting-state functional MRI, default mode (DMN) subnetwork, psychosis, tobacco

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INTRODUCTION

Cigarette smoking is the leading cause of preventable death in the United States (1). In schizophrenia, the prevalence of smoking is over 60% (2), three-times higher than the general population (3). Tobacco use is the top preventable cause of early mortality in schizophrenia due to its associated cardiovascular disease, lung cancer, and respiratory illness (4). However, a biological explanation for the prevalence of smoking in schizophrenia has remained elusive.

There are several hypotheses for the increased prevalence of smoking in schizophrenia. One is that individuals with schizophrenia have a vulnerability to smoking due to biological overlap between schizophrenia-related pathology and processes involved in nicotine dependence (5, 6). Neuroimaging has provided partial support for this hypothesis. There have been abnormalities identified in the insula, dACC, and striatum in both schizophrenia and in nicotine dependent neurotypical individuals (7–9).

An alternative hypothesis is that nicotine use in schizophrenia is a method of "self-medicating" to correct schizophrenia pathology (10). Nicotine can enhance cognitive processes in smokers, non-smokers, and in those with schizophrenia (11–13). One proposed explanation is that nicotine use in schizophrenia is motivated by a need to correct the cognitive deficits of this disorder. This theory remains speculative because of a lack of evidence directly linking nicotine consumption to the biological processes underlying its cognitive benefit. To support a causal relationship between cognition and tobacco use, a common biological substrate needs to be (a) linked to cognition, (b) impaired in schizophrenia, and (c) acted upon by nicotine.

We sought to identify brain network pathology that could uniquely explain the prevalence of nicotine dependence among individuals with schizophrenia. The challenge is that there is a paucity of large imaging datasets in psychotic disorders that also includes detailed information about nicotine use. Similarly, studies of nicotine administration have largely focused on brain regions defined a priori or limited to regions responsive to the tasks employed (14). Critically, cross-sectional studies linking connectivity to smoking require validation of those same circuits e.g., with nicotine administration. These study constraints therefore require more selective datasets which have been intended to examine these circuits.

We utilized existing resting-state fMRI data from two independent cohorts (14–16) using an entirely *data-driven* approach. We sought to identify brain regions where functional connectivity correlates with nicotine use. This approach consists of two steps: in the first, multivariate distance matrix regression (MDMR) is used to identify brain regions where global connectivity correlates with nicotine use, then the identified region is used as a seed to determine the spatial pattern of how connectivity to this region varies with nicotine use (17). This spatial pattern of connectivity corresponded to specific brain networks. Based on these findings, we then tested nicotine's causal influence on these defined networks in a second, independent cohort of individuals. In this cohort, individuals with schizophrenia and controls received an acute dose of nicotine in a randomized, placebo-controlled crossover design (14).

We observed that severity of nicotine use in schizophrenia is strongly linked to individual variation in topography (18) of the default mode network (DMN) and this relationship is schizophrenia-specific i.e., not observed in neurotypical control smokers. Having observed an association between cigarette consumption and the DMN, we hypothesized that nicotine has a direct impact on that network. After considering which network features could be (1) modulated by nicotine and (2) experimentally measured, we hypothesized that nicotine affects within-network functional connectivity. We therefore sought to test the ability of nicotine to acutely modulate network connectivity in an independent cohort. In this cohort, we determined that nicotine can modulate connectivity in the DMN, thereby reversing schizophrenia-specific abnormalities and providing causal evidence for a biological basis for increased nicotine use in schizophrenia.

MATERIALS AND METHODS

Participants

Cohort 1: In this cohort, we sought to identify brain circuits associated with nicotine dependence in schizophrenia and control individuals using a data-driven approach. Eighteen nicotine-dependent individuals with schizophrenia ($n = 15$) or schizoaffective disorder ($n = 3$) were recruited from McLean Hospital. Seventeen control nicotine-dependent participants were recruited from the community. Participants were 18–55 years old and provided informed consent approved by the McLean Hospital IRB. Participants were matched on gender and nicotine dependence severity (as measured by Fagerstrom Test for Nicotine Dependence [FTND]). To be included, participants reported smoking >10 cigarettes per day for at least 6 months, FTND of at least 4, and expired air carbon monoxide (CO) level of 10 ppm or greater. Individuals were excluded if they reported current substance abuse within the past 6 months, as defined by SCID-IV. All subjects were required to have a negative urine toxicology and pregnancy tests, and no recent alcohol use as measured by a breathalyzer.

Cohort 2: In Cohort 2, we sought to determine if nicotine causally affects the brain circuits we identified in Cohort 1 as associated with nicotine dependence. Twelve participants with schizophrenia and 12 control participants, aged 18–55 years old, right-handed were recruited from the community. Written, informed consent for a protocol approved by the Massachusetts General Hospital and McLean Hospital Institutional Review Boards was obtained from each participant. Control participants were excluded if they reported a history of a first-degree relative with a psychotic disorder. All participants were required to have negative urine toxicology screens at all study visits. Individuals with a history of neurological disorders or head injury with neurological sequelae were excluded. Expired CO was used to confirm smoking status (CO < 5 ppm for non-nicotine-dependent, $n = 16$; CO > 10 ppm for nicotine-dependent, $n = 8$).

In both cohorts, diagnosis of schizophrenia or schizoaffective disorder and absence of Axis I diagnoses in controls was confirmed by Structured Clinical Interview for DSM-IV (SCID-IV) (19). Participants were not undergoing treatment for nicotine dependence.

Demographic, smoking, and clinical characteristics for each cohort are presented in **Tables 1**, **2**. In Cohort 1, participants with schizophrenia were significantly older than controls ($p < 0.01$). Although groups were matched on FTND, nicotine-dependent individuals with schizophrenia had significantly greater lifetime cigarette use ($p < 0.05$). In Cohort 2, there were more current nicotine-dependent individuals in the schizophrenia group (6/12, 50%) than the control group (2/12, 17%), although this was not statistically significant ($p = 0.08$).

TABLE 1 | Cohort 1: Demographics and clinical data.

	Control ($n = 17$)		Schizophrenia ($n = 18$)		*t*	*df*	*p*
	Mean	**SD**	**Mean**	**SD**			
Age	30.8	5.6	38.6	9.7	−2.9	27	0.007*
Gender (F/M)	8/9		9/9		$\chi2 = 0.030$	1	0.86
Education (years)	14.4	2.4	12.9	2.4	1.9	33	0.06
Cigarettes per day	13.4	3.8	16.3	7.9	−1.3	25	0.19
FTND	5.4	1.4	5.7	1.1	−0.85	31	0.40
Lifetime cigarette use (pack years)	9.1	5.5	15.1	10.3	−2.2	26	0.04*
BPRS total score			48	13.5			
Chlorpromazine equivalents (mg/day)			539	504			

FTND, fagerstrom test for nicotine dependence; BPRS, brief psychiatric rating scale.
**Statistically significant.*

TABLE 2 | Cohort 2: Demographics and clinical data.

	Control ($n = 12$)		Schizophrenia ($n = 12$)		*t*	*df*	*p*
	Mean	**SD**	**Mean**	**SD**			
Age	38.8	10.7	36.5	7.9	0.61	20	0.55
Gender (F/M)	6/6		4/8		$\chi2 = 0.69$	1	0.41
Education (years)	15.1	2.2	14.0	2.2	1.25	22	0.22
Current nicotine dependence	2 (16.7%)		6 (50.0%)		$\chi2 = 3$	1	0.08
Cigarettes per day	14	5.7	12	7.4	0.47	2.3	0.68
FTND	5	1.4	5	1.7	0	2.1	1
Lifetime cigarette use (pack years)	6.9	6.9	10.2	9.9	−0.54	2.6	0.63
Nicotine dose (mg)	14	6.0	16.3	6.2	−0.94	22	0.36
BPRS total score			37.5	11.2			
Chlorpromazine equivalents (mg/day)			406	316			

FTND, fagerstrom test for nicotine dependence; BPRS, brief psychiatric rating scale.
**Statistically significant.*

Clinical Assessments

Smoking behavior was assessed, including cigarettes smoked per day. Severity of nicotine dependence was measured using the FTND. Symptom severity was assessed in participants with schizophrenia using the Scale for Assessment of Negative Symptoms (SANS) and Brief Psychiatric Rating Scale (BPRS). Craving was assessed using the Tiffany Questionnaire of Smoking Urges (QSU), and withdrawal was measured using the Minnesota Nicotine Withdrawal Scale (MNWS).

Study Design

Cohort 1: In this observational study, participants underwent resting-state fMRI and clinical characterization including daily tobacco use (15, 16).

Cohort 2: A randomized, double-blind, placebo-controlled, crossover design was utilized in which each participant was administered either transdermal nicotine or identical placebo patch on two separate study sessions performed at least 7 days apart (14). The order of drug was counterbalanced within each group (schizophrenia, control). Participants received different doses of nicotine depending on smoking status (nicotine-dependent individuals were dosed based on packs per day to avoid withdrawal, range 14–28mg). Non-nicotine-dependent individuals initially received 14 mg but due to adverse events of nausea and vomiting (participants excluded from analysis, as in 13), the dose for non-nicotine-dependent individuals was reduced to 7 mg in five participants. Three hours after patch application, participants underwent resting-state fMRI. This time interval was chosen to coincide with peak serum nicotine concentrations (20) and to avoid peak withdrawal symptoms, which typically occur 6–12 h after smoking cessation (21). Craving, withdrawal, mood, and anxiety were assessed before and after each patch administration and after each MRI scan.

Imaging Analysis

MRI Data Acquisition

We analyzed existing data from two independent neuroimaging studies, so the MRI acquisition parameters were different for each cohort.

Cohort 1: Participants in Cohort 1 were scanned on a 3-T Siemens Trio scanner with a 32-channel head coil at McLean Imaging Center. Multi-planar rapidly acquired dual echo gradient-echo structural images used the following parameters: TR = 2.1 s, TE = 3.3 ms, slices = 128, matrix = 256 x 256, flip angle = 7°, resolution = 1.0 × 1.0 × 1.33 mm. The 6-min resting-state acquisition used the following parameters: 144 volumes, TR = 2.5 s, TE = 30 ms, slices = 42, flip angle = 90°, field of view = 448 × 448 mm^2, and voxel size = 3.5 mm isotropic. Participants were asked to remain awake and to keep their eyes open for the duration of the scan.

Cohort 2: Participants in Cohort 2 were scanned on a 3-T Siemens Trio scanner with a 32-channel head coil at McLean Imaging Center. High resolution (1 × 1 × 1 mm^3) T1-weighted MPRAGE images were acquired. During resting-state acquisition, participants were instructed to rest with eyes open for

6.2 min. Functional MR images were acquired with interleaved acquisition tilted −30° from the AC-PC line using a gradient-echo echoplanar imaging (EPI) sequence. Resting state data acquisition used the following parameters: 124 volumes, TR = 3 s, TE = 30 ms, slices = 47, flip angle = 85°, field of view = 504 × 504 mm^2, and voxel size = 3.0 mm isotropic.

MRI Data Processing

All analyses were preprocessed using the DPABI toolbox (Data Processing and Analysis for Brain Imaging (22); http://rfmri.org/dpabi). As a quality control metric, data from any participant whose scans exceeded motion thresholds (3 mm translation or 3° rotation) were discarded. Individual time points with framewise displacement 0.5 mm were removed via scrubbing (23), and scans with 50% of volumes removed for framewise displacement were discarded. All data were preprocessed to remove motion (24-parameter), CSF signals, white matter signals, global signal, and overall linear trend. A bandpass filter was applied (0.01–0.08 Hz). Data were normalized using the DARTEL toolbox into Montreal Neurological Institute (MNI) space and smoothed with an 8-mm full-width half-maximum kernel. Analyses were conducted in a gray matter mask defined within the group.

Cohort 1: Network Discovery Using Multivariate Distance Matrix Regression

We conducted an assessment across all participants regardless of group (schizophrenia and controls) to identify shared and diagnosis-specific circuits of nicotine use. A multivariate pattern analysis of whole-connectome data (MDMR) was used to identify the strongest links between daily cigarette consumption and functional connectivity (17). This analysis occurs in two steps: the first step identifies any regions where daily cigarette consumption correlates with functional connectivity, and the second step (*post-hoc* testing) involves seed-based analysis of the identified region (see *ROI-Based Connectivity Analysis*) to determine the spatial pattern of connectivity it represents (17, 24, 25).

After preprocessing, resting-state fMRI data were analyzed with MDMR (**Figure 1**) (17). This method allows for an unbiased,

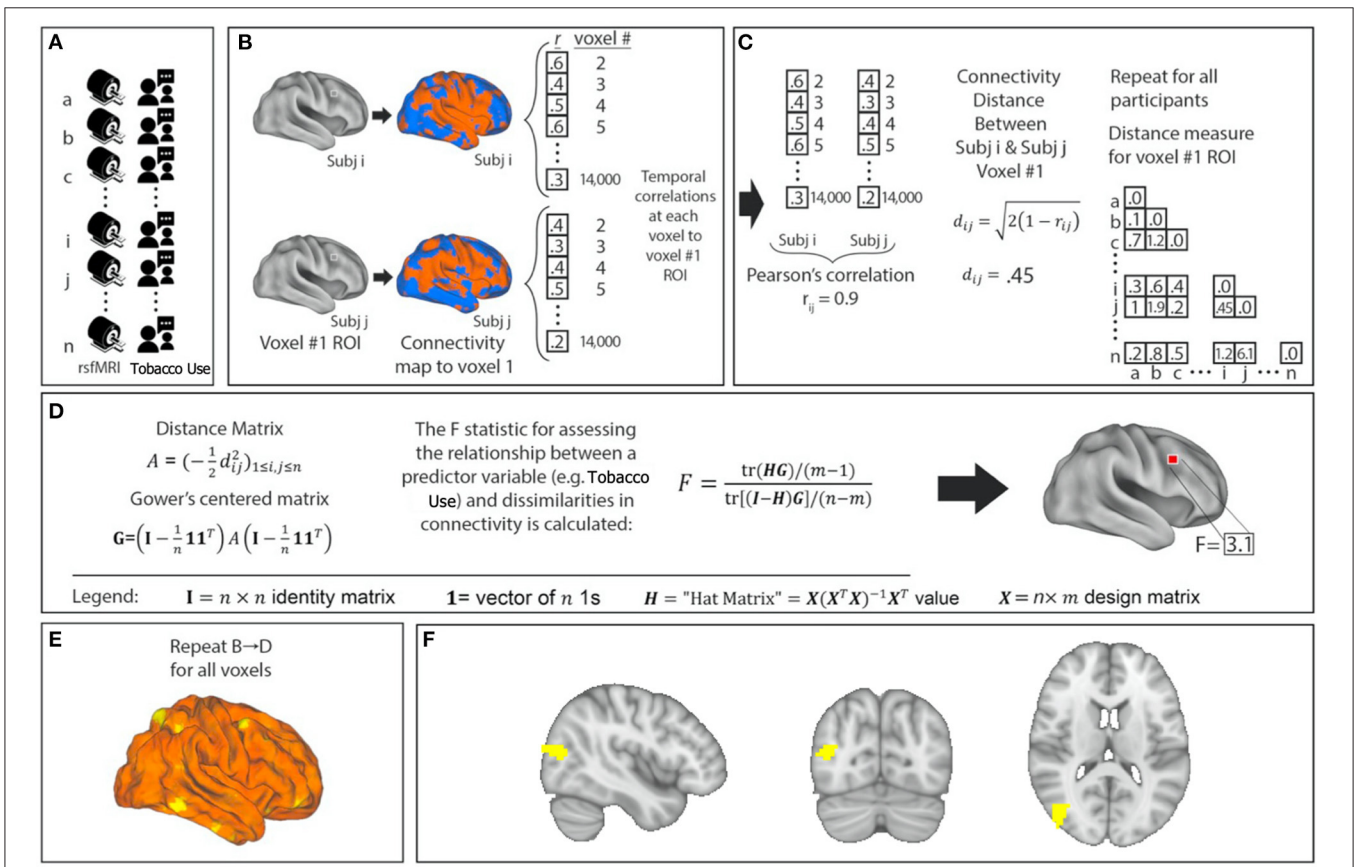

FIGURE 1 | Network identification using Multivariate Distance Matrix Regression (MDMR). Cigarette consumption and resting-state functional MRI (rsfMRI) data were collected for each participant **(A)**. For each voxel in the brain, the voxel was used as a seed region to create a connectivity map for each participant **(B)**. These maps were compared with each other to create a subject-wise similarity matrix **(C)**. Daily cigarette consumption for each participant was then combined with the connectivity similarity matrix to produce a pseudo-F statistic, which characterizes how individual variation in cigarette consumption explains individual variation in functional connectivity **(D)**. This is repeated for all voxels **(E)**. Each MDMR voxel-wise result was then combined to produce a map of the ability of the connectivity pattern to predict a cigarette consumption score in each voxel **(F)**. A permutation test of the study subjects' labels can be used to test the significance of this pseudo-F statistic.

data-driven approach to identifying phenotype-connectivity relationships. MDMR allows quantification of how a variable of interest (daily cigarette use here) is reflected in the distributed connectivity of individual voxels to the whole brain (i.e., at the finest resolution possible) without parcellating the brain into regions defined a priori (**Figure 1**). In brief, MDMR tests every voxel to determine if whole-brain connectivity to that voxel is more similar in individuals with similar values on an independent measure (daily cigarette consumption, cigarettes/day) than in individuals with dissimilar values. As described previously, MDMR occurs in several stages: First, scan and cigarette consumption measurements are collected from all participants (**Figure 1A**). Functional connectivity was calculated in the following way: a seed-to-voxel functional connectivity map is generated for each participant. These functional connectivity maps are correlated by calculating the temporal Pearson's correlation coefficients between each voxel, using its BOLD signal time-course, and all other gray matter voxels using a standardized gray matter mask included in the DPABI toolbox (**Figure 1B**). The temporal correlation coefficients for each voxel in the functional connectivity map are then correlated with the values of corresponding voxels in the maps generated for the other participants. This Pearson's correlation coefficient, *r*, is a measure addressing how similar the whole-brain functional connectivity to a specific voxel is, for each voxel, between patients. This value is used to calculate between-subject distance (or dissimilarity) using the metric $d_{ij} = \sqrt{2\left(1 - r_{ij}\right)}$ where i and j are two subjects and r is the correlation coefficient above (**Figure 1C**). Third, we test the relationship between the independent variable of interest, here, daily cigarette consumption (cigarettes/day), and the inter-subject distances in connectivity generated at the previous stage. Broadly speaking, this process consists of an ANOVA-like hypothesis test between a variable of interest and a matrix of distances. This method was originally named multivariate distance matrix regression to study associations between gene expression and related variables. Shehzad et al. (17) adapted this method to test the relationship between variables of interest and a matrix of distances, the matrix being similarity between subject's whole-brain functional connectivity. This test first creates a distance matrix $A = (-\frac{1}{2}d_{ij}^2)_{1\leq i,j\leq n}$ among n participants where d = the between-subject distance metric calculated above. Next, this matrix is used to create a Gower's centered matrix $G = \left(I - \frac{1}{n}11^T\right)A\left(I - \frac{1}{n}11^T\right)$, in which n is the number of participants, I is the $n \times n$ identity matrix, and 1 is a vector of n 1s. The F statistic for assessing the relationship between a predictor variable (e.g., daily cigarette consumption, cigarettes/day) and dissimilarities in connectivity is calculated as follows: For m predictor values, let $\boldsymbol{X}$ be a $n \times m$ design matrix of predictor values, and let $H = X(X^TX)^{-1}X^T$ be the associated $n \times m$ "hat" matrix.

$F = \frac{tr(HG)/(m-1)}{tr[(I-H)G]/(n-m)}$ (**Figure 1D**). This process is repeated for every voxel. The result is a whole-brain map showing how significant the relationship between daily cigarette consumption measurements and functional connectivity is at every voxel (**Figure 1E**). From this generated map, ROIs for follow-up analysis are determined based on clusters of significant voxelwise F-statistics. To correct for multiple comparisons, a nonparametric permutation is calculated for voxels that exceed the significance threshold of $p < 0.001$ and clusters of such with an extent threshold of $p < 0.05$, with a null distribution calculated from 5,000 such permutations (17). This voxelwise threshold was selected to maximize the replicability potential. This approach has been used to examine the relationship between psychiatric pathology and connectivity (24, 25). We modeled the effect of daily cigarette consumption on functional connectivity while covarying for effects of chlorpromazine equivalents, age, and sex (**Figure 1F**). After the initial whole group analysis, we repeated this analysis for the schizophrenia group and the control group independently.

We conducted the MDMR analysis to identify anatomical regions where connectivity significantly varied with nicotine consumption. After identifying any MDMR regions, we then conducted follow-up seed-based connectivity (see *ROI-Based Connectivity Analysis*) analysis to examine the spatial distribution of these connectivity differences as in prior MDMR analyses (17, 26–28).

Importantly, MDMR identifies regions where connectivity correlates to a phenotype (e.g., daily cigarette consumption, cigarettes/day) but this initial analysis does not identify the direction of correlation or the spatial pattern. This process disregards spatial information about the voxels that gave rise to between-individual distances e.g., Two individuals may be very distant (dissimilar) in the functional connectivity of a single voxel in the parieto-occipital region, but is their dissimilarity driven by differences in parieto-occipital connectivity to the temporal lobes or medial prefrontal cortex or all of the above? The first step of MDMR does not display this information (17). In order to visualize this spatial information requires follow-on seed-based connectivity analysis. Shehzad et al. and others have termed this follow-on analysis "*post-hoc*" testing to make clear that this should not be considered independent hypothesis testing nor should it be considered independent validation of the original MDMR finding (17, 26–28).

ROI-Based Connectivity Analysis

To visualize spatial patterns of connectivity driving the results of MDMR, maps of connectivity to the region identified in MDMR were generated. This step identifies the spatial pattern of connectivity to the region identified in the MDMR analysis (17, 26–28). The time course of the BOLD signals from rsfMRI scans in the ROI identified in the MDMR process was extracted and whole brain connectivity maps were generated using DPABI. Using SPM12 ("SPM–Statistical Parametric Mapping," http://www.fil.ion.ucl.ac.uk/spm) we regressed the z-transformed Pearson's correlation coefficient connectivity maps against daily cigarette consumption to generate spatial maps of how whole functional brain connectivity to the ROI varies with cigarette consumption. We measured ROI to ROI connectivity at this step by measuring BOLD correlation between an ROI defined by the MDMR-identified region and a DMN ROI (29). We then correlated connectivity between the MDMR-identified ROI and the identified brain networks with daily cigarette consumption.

Cohort 2: Network Effects of Acute Nicotine Administration

Whole-Network Connectivity Values

In Cohort 1, we observed a relationship between a pathologically expanded DMN topography and greater daily nicotine use. Based on this observation, we hypothesized that nicotine has a direct effect on the DMN. After considering which network features could be both modulated by nicotine and measured experimentally, we hypothesized that nicotine affects within-network functional connectivity. We therefore sought to test the ability of nicotine to acutely modulate DMN connectivity in an independent cohort. To test this hypothesis, we compared within-DMN mean functional connectivity at nicotine and placebo administration. We generated individual values of mean DMN functional connectivity by placing 6 mm spheres at coordinates that correspond to seven standard nodes of the DMN (posterior cingulate/precuneus, medial prefrontal, left lateral parietal, right lateral parietal, left inferior temporal, right inferior temporal, medial dorsal thalamus) [see (30) for coordinates]. The time course of the BOLD signals from the ROIs were correlated with each other and z-transformed to generate a 7 × 7 ROI to ROI connectivity matrix. A mean connectivity from this matrix was generated for each participant under each condition (nicotine or placebo). The output from this analysis was a mean connectivity value for the entire DMN for each participant at nicotine administration ($FC_{nicotine}$) and at placebo administration ($FC_{placebo}$). Change in whole-network functional connectivity ($FC_{nicotine} - FC_{placebo}$) was calculated for each participant.

Statistical Analyses

We correlated change in whole-network functional connectivity ($FC_{nicotine} - FC_{placebo}$) with nicotine dose. We calculated Pearson correlation coefficients between measurements of functional connectivity and clinical variables. We used paired *t*-tests to compare change in connectivity between nicotine and placebo administration. We used a mixed effects repeated measures ANOVA to determine the effect of diagnosis, smoking status, and drug on changes in connectivity.

RESULTS

Resting-State Network Organization Predicts Cigarette Consumption

Multivariate pattern analysis of the whole-connectome of Cohort 1 (18 schizophrenia, 17 controls) identified a single region (Cluster $k = 77$, centered at MNI $\times = 42$, $y = -78$, $z = 18$) in the right parieto-occipital region where functional connectivity correlated with daily cigarette consumption (**Figure 2A**). When we repeated this analysis in each group (i.e., in schizophrenia alone and controls alone) we observed a significant relationship between connectivity and cigarette

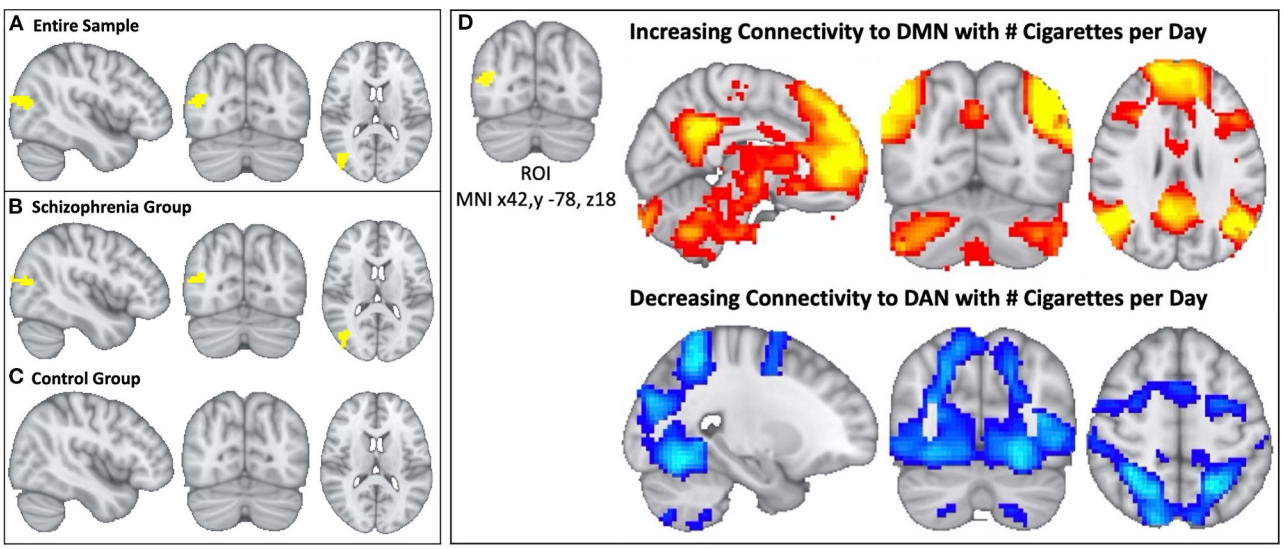

FIGURE 2 | In schizophrenia, individual variation in DMN topography is linked to cigarette consumption: higher cigarette consumption is linked to both increased connectivity between parieto-occipital ROI and DMN and decreased connectivity between parieto-occipital ROI and the DAN. We identified a parieto-occipital region (Thresholded voxelwise $p < 0.001$, Cluster $k = 77$, MNI x42, y −78, z18, $p < 0.05$) where functional connectivity correlates with daily cigarette use in our combined sample of schizophrenia and control smokers **(A)**. In this region, increased functional connectivity correlates with greater daily cigarette consumption. We repeated this analysis in each diagnostic sub-group and observed a significant relationship between connectivity and cigarette use in the schizophrenia group (Cluster $k = 52$, $p < 0.05$) **(B)** but not in the neurotypical group **(C)**. After identifying the parieto-occipital region where functional connectivity correlated with daily cigarette use, we conducted follow-up seed-based connectivity analysis to examine the spatial pattern of how connectivity to this region correlates with nicotine consumption in the schizophrenia group. We observed that global functional connectivity to this region was positively correlated with the DMN and negatively correlated with the DAN **(D)**, which was readily apparent by visual inspection. Higher cigarette consumption was linked to both increased connectivity between the parieto-occipital ROI and DMN and decreased connectivity between the parieto-occipital ROI and the DAN.

consumption in the schizophrenia group ($n = 18$, Cluster $k = 52$, **Figure 2B**) but no such relationship in the control group ($n = 17$, **Figure 2C**). This was observed despite the fact that groups were matched for severity of nicotine dependence. Further, there were no significant group-level differences in head motion ($p = 0.99$).

In the follow-up analysis to determine the spatial pattern of how connectivity to the right parieto-occipital region correlates with nicotine consumption, we observed that functional connectivity to this identified region is positively correlated with the DMN and negatively correlated with the dorsal attention network (DAN) in the schizophrenia group ($n = 18$, **Figures 2D**, **3A**). We observed a linear relationship where greater daily cigarette consumption was significantly correlated with greater connectivity to the DMN (**Figure 3A**, $r = 0.77$, $p < 0.001$). Notably, this linear relationship extended across both positive (correlation) and negative (anti-correlation) connectivity values. To elaborate: In some individuals activity in this MDMR identified region was correlated with the DMN (and anticorrelated with DAN) while in other individuals this region was correlated with DAN (and anticorrelated with DMN). This is consistent with spatial distribution (topography) of these networks co-varying with cigarette consumption in the schizophrenia group ($n = 18$, **Figure 3**). In an individual diagnosed with schizophrenia who smokes heavily, this parieto-occipital region was part of the DMN and not part of the DAN (**Figure 3B**). In a light smoking individual with schizophrenia, this relationship was reversed: the parieto-occipital region was instead part of the DAN and was external to the DMN (**Figure 3C**). In summary, with increasing daily cigarette consumption, this parieto-occipital region was increasingly likely to be a part of the DMN and less likely to be connected to the DAN, suggesting a difference in the *topography* of these two resting-state networks. Thus, we observed that individual-level differences in the spatial organization (i.e., topography) of the DMN and DAN in this region reflected individual variation in daily cigarette consumption in the schizophrenia group. In a large sample of healthy young adults, this parieto-occipital region is typically a part of the DAN, suggesting that the extension of the DMN into this region in heavy smokers with schizophrenia represents schizophrenia-specific pathologic organization (29).

To summarize, in schizophrenia, the strongest functional connectivity correlate of nicotine consumption in the brain is driven by variation in the topography of resting-state networks. In participants diagnosed with schizophrenia, individual variation in the spatial arrangement of these networks is linked

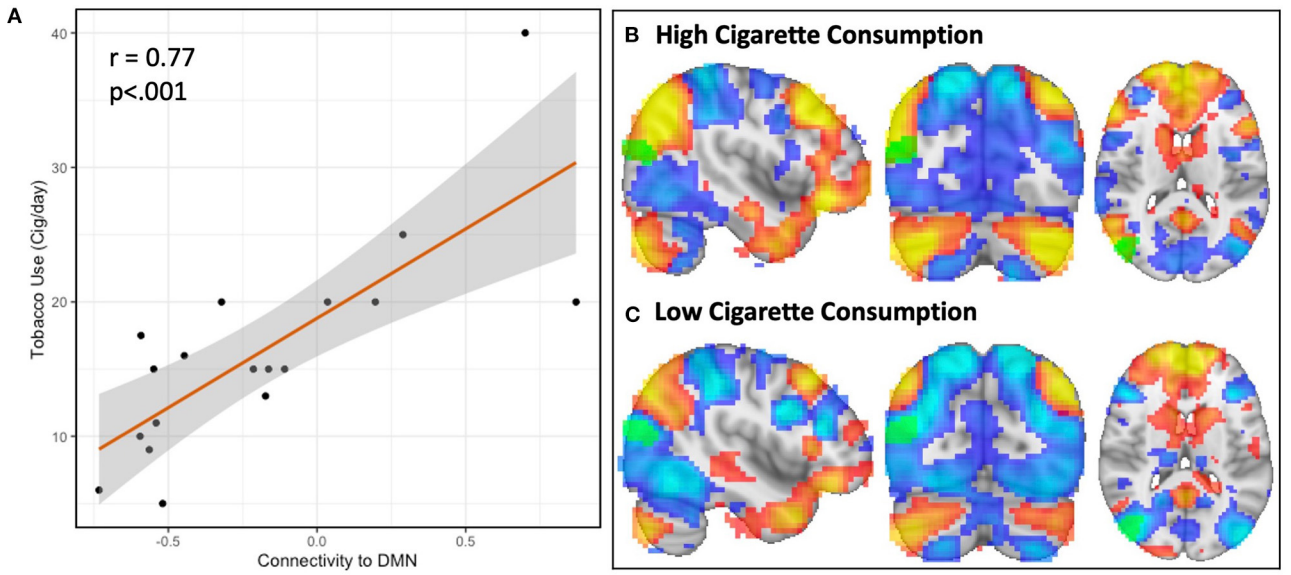

FIGURE 3 | Resting-state network topography is strongly linked to cigarette consumption in schizophrenia. The spatial organization of resting-state networks is strongly linked to cigarette consumption in schizophrenia. In the first step of MDMR, we identified a parieto-occipital region where functional connectivity correlated with daily tobacco use (**Figure 1**). In order to determine the direction and spatial pattern of connectivity to this parieto-occipital region, we conducted follow-up seed-based analysis within the schizophrenia cohort. This region was connected to the default mode network (DMN), which was readily identified by visual inspection. We therefore measured the functional connectivity between our MDMR-identified region and the DMN. When we compared tobacco use (cigarettes per day) with connectivity to the DMN, we observed a linear relationship where greater daily cigarette consumption was significantly correlated with greater connectivity to the DMN [**(A)**, $r = 0.77$, $p < 0.001$]. This indicates that, with increasing daily cigarette consumption, the identified parieto-occipital region is increasingly connected to the DMN rather than to other networks. We determined this relationship was due to the topography of the DMN, as evidenced by two representative individuals **(B,C)**. Displayed here are the DMN (red) and dorsal attention network (DAN, blue) in two example individuals diagnosed with schizophrenia with either high **(B)** (40 cigarettes/day) and low **(C)** (5 cigarettes/day) cigarette consumption. In an individual with high daily cigarette consumption (3B), the DMN extends into the parieto-occipital region identified using MDMR ($k = 52$, MNI x = 42, y = −78, z = 18, green) while the DAN does not; in an individual with low daily cigarette consumption **(C)**, the DMN is external to this region and this region is part of the DAN. This link between network topography and cigarette consumption was not observed in a comparison group of nicotine-dependent controls.

to individual variation in nicotine consumption. Specifically, with greater daily cigarette consumption, we observed an expansion of the DMN into territory normally occupied by the DAN. This relationship between topography and nicotine use was not observed in neurotypical controls.

The Relationship Between Acute Nicotine Administration and DMN Connectivity

In the first cohort we observed a strong relationship between cigarette use and the spatial organization of the DMN. This relationship was linearly related to the amount of daily nicotine use in participants diagnosed with schizophrenia such that greater daily cigarette use was associated with increased connectivity to the DMN (**Figure 3A**) and a pathologically expanded topography of the DMN (**Figures 3B,C**). However, the directionality of this association was unclear and had several different interpretations (see Discussion). We therefore sought to test if nicotine had a direct effect on DMN resting-state connectivity using an independent second dataset (Cohort 2).

Acute nicotine administration has been observed to decrease activity in the DMN during a task (31) and at rest (32). Therefore, we hypothesized that (1) nicotine would acutely affect the temporal correlation of spontaneous activity (i.e., functional connectivity) of the DMN in a dose-dependent manner and (2) this effect would preferentially affect participants with schizophrenia. In Cohort 2, 24 participants (12 SZ, 12 HC) were enrolled in a randomized, placebo-controlled crossover study of transdermal nicotine patch (**Table 2**). Participants underwent resting-state fMRI and clinical characterization at each timepoint as described in Materials and Methods.

After generating an entire DMN-network measurement of functional connectivity using seven ROIs defined as part of the DMN, we measured whole DMN functional connectivity change in Cohort 2 in relation to nicotine dose across the combined sample ($n = 24$). We observed a linear relationship between higher nicotine dose and greater reduction in DMN connectivity ($R = -0.50$, 95% CI -0.75 to -0.12, $p = 0.012$) (**Figure 4**).

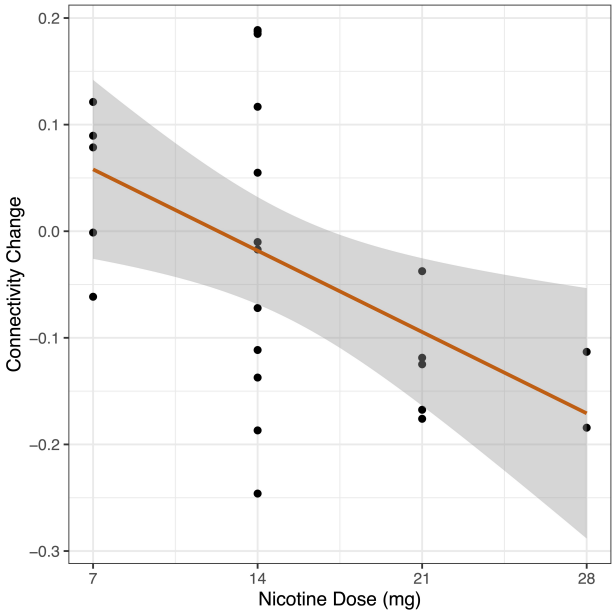

FIGURE 4 | Dose-response relationship between nicotine and DMN connectivity change. In a cohort of schizophrenia and control participants, we measured whole DMN functional connectivity twice: once in the placebo condition and once with nicotine patch. Change in whole DMN functional connectivity was calculated between these two administrations ($FC_{nicotine} - FC_{placebo}$). Dosage of nicotine patch varied between individuals based on smoking status (nicotine-dependent, $n = 8$, range 14–28 mg; non-nicotine dependent, $n = 16$, range 7–14 mg). We correlated DMN network connectivity change to administered nicotine dose across the combined sample ($n = 24$). We observed a linear relationship between increased nicotine dose and greater reduction in DMN connectivity across the entire sample ($r = -0.50$, $p = 0.012$).

Sensitivity Analyses

Given our mixed sample of nicotine-dependent ($n = 8$) and non-nicotine dependent ($n = 16$) individuals in Cohort 2 and the potential confounding effect of nicotine withdrawal symptoms, we performed correlations between ratings of nicotine withdrawal among nicotine-dependent participants and DMN connectivity. DMN connectivity did not correlate with post-scan nicotine withdrawal at the placebo ($R = 0.37$, 95% CI -0.53 to 0.88, $p = 0.42$) or nicotine timepoint ($R = -0.11$, 95% CI -0.76 to 0.64, $p = 0.80$). There was no correlation between change in DMN connectivity and change in post-scan withdrawal symptoms ($R = 0.17$, 95% CI -0.67 to 0.82, $p = 0.72$). When we controlled for post-scan withdrawal symptoms between change in DMN connectivity and nicotine dose, there was no significant partial correlation ($r = -0.17$, test statistic $= -0.35$, $p = 0.75$). There was a main effect of drug on head motion, such that there was less head motion with nicotine administration ($p = 0.02$). However, there were no significant differences in head motion between participants with schizophrenia and controls at nicotine ($p = 0.49$) or placebo ($p = 0.84$) conditions, nor were there any no group x drug effects on head motion ($p = 0.61$). Further, there was no effect of smoking status on head motion ($p = 0.34$). In summary, our findings do not appear to be driven by potential withdrawal symptoms during the placebo condition. This is consistent with the study protocol, which was designed to avoid peak withdrawal symptoms. Indeed, reported withdrawal was minimal, and there was no difference between median post-scan withdrawal scores at nicotine (2/24) or placebo administration (2/24).

After observing significant effects of nicotine on global DMN connectivity in Cohort 2, we interrogated connectivity between individual nodes of the DMN to determine if the network-wide effect was driven by region-specific alterations in connectivity. We did not identify any specific nodes in the DMN that explained this result (**Table 3**). Nicotine dose was correlated with a generalized decrease in connectivity across the entire DMN. There was a significant correlation between change in DMN connectivity and nicotine dose between seeds in the precuneus/PCC and bilateral temporal lobes ($p < 0.05$), but this does not survive correction for multiple comparisons.

TABLE 3 | Node-specific correlation values of DMN connectivity change and nicotine dose.

	Precun/PCC	mPrefrontal	Lparietal	Rparietal	Ltemporal	Rtemporal	mdThalamus
Precun/PCC	–	−0.19	−0.20	−0.20	−0.41*	−0.48*	−0.17
mPrefrontal	−0.19	–	−0.13	−0.27	−0.21	−0.39	−0.17
Lparietal	−0.20	−0.13	–	−0.26	−0.38	−0.38	−0.07
Rparietal	−0.20	−0.27	−0.26	–	−0.23	−0.23	−0.14
Ltemporal	−0.41*	−0.21	−0.38	−0.23	–	−0.14	0.24
Rtemporal	−0.48*	−0.39	−0.38	−0.23	−0.14	–	−0.29
mdThalamus	−0.17	−0.17	−0.07	−0.14	0.24	−0.29	–

*Precun/PCC, precuneus and posterior cingulate cortex; mPrefrontal, medial prefrontal; Lparietal, left parietal; Rparietal, right parietal; Ltemporal, left temporal; Rtemporal, right temporal; mdThalamus, medial dorsal thalamus. Pearson correlation coefficients were calculated and Z-transformed. *$p < 0.05$ uncorrected.*

Diagnosis-Specific Effects of Nicotine on Default Mode Network Connectivity

We then considered if the effect of nicotine on DMN connectivity in Cohort 2 was more pronounced in schizophrenia ($n = 12$) compared to controls ($n = 12$).

During the placebo condition in Cohort 2, there was a significant effect of diagnosis on mean whole-DMN connectivity. We observed mean whole-DMN hyperconnectivity in schizophrenia compared to controls (0.44 vs. 0.32, $p < 0.05$), consistent with prior findings in schizophrenia (33). However, during nicotine administration, DMN connectivity was no longer significantly different between groups (0.37 vs. 0.32, $p = 0.19$) (**Figure 5**).

We observed evidence that nicotine dose had a significant effect on DMN connectivity which was more pronounced in schizophrenia in Cohort 2. A mixed-effects repeated measures ANOVA was performed to assess the interaction of diagnosis, smoking status, and drug (nicotine vs. placebo) on DMN connectivity. The schizophrenia group had significantly higher DMN connectivity ($p < 0.05$) than controls. There was a trend-level interaction between diagnosis and smoking on DMN connectivity ($p = 0.09$), where smoking and schizophrenia diagnosis both increased DMN connectivity. There was no significant effect of drug order.

DISCUSSION

We identified a novel brain basis for the high prevalence of nicotine dependence in schizophrenia. We observed that variation in nicotine consumption is linked to the spatial organization of two resting-state networks, the DMN and the DAN in a right parieto-occipital region. Specifically, higher amounts of daily tobacco consumption were linked to expansion of the DMN into territory normally occupied by DAN in healthy controls (29). This relationship between tobacco consumption and topography was observed only in participants with schizophrenia. Individual differences in network topography have been previously observed (18, 34–39). Only recently have these topographic variations been linked to behavioral/cognitive phenotypes (24, 25, 40). Our report of a link between network topography and substance use in schizophrenia is novel.

There are several possible interpretations for the association between DMN/DAN network organization and tobacco consumption. One explanation is that tobacco use changes brain network spatial organization. This is unlikely, as such an explanation would presumably be observed in both neurotypical nicotine using individuals and in those with schizophrenia, which was not observed in the current study. Given the link between nicotine use and network topography was found only in those with schizophrenia, it is more likely that the pathophysiology of schizophrenia changes the organization of the DMN. The observable result of this is (1) previously described DMN within-network hyperconnectivity in schizophrenia and (2) changes in network spatial organization observed in our sample. Nicotine may correct DMN within-network hyperconnectivity such that individuals with schizophrenia are drawn to smoking and therefore use in doses that are commensurate with the degree of network disruption.

If the degree of network pathology leads to cigarette smoking proportional to underlying pathology, then acute nicotine would be expected to (1) have a direct effect on the network and (2) demonstrate a dose-response relationship between nicotine dose and network connectivity. In order to differentiate these possible explanations, we investigated the effects of acute nicotine administration on DMN connectivity.

We examined the effect of acute nicotine administration on the DMN and observed a dose-response relationship between nicotine dose and DMN connectivity (**Figure 4**). Although it has been previously observed that acute nicotine administration decreases DMN activity in nicotine-dependent individuals (31) and decreases DMN connectivity in non-smoking controls (32), a dose-response curve has not been reported. The nicotine-induced reduction in DMN connectivity occurred across the entire network rather than being driven by an individual node of the DMN. We then examined differences in DMN connectivity by diagnosis. Participants with schizophrenia demonstrated DMN hyperconnectivity, a finding consistent with existing literature (33). This diagnosis-specific increased DMN connectivity was no longer significant after acute nicotine administration, consistent with a theory in which DMN network pathology is an underling cause of nicotine use in schizophrenia. We observed that nicotine administration was associated with a greater reduction of DMN connectivity in the schizophrenia group than the control group, a trend-level

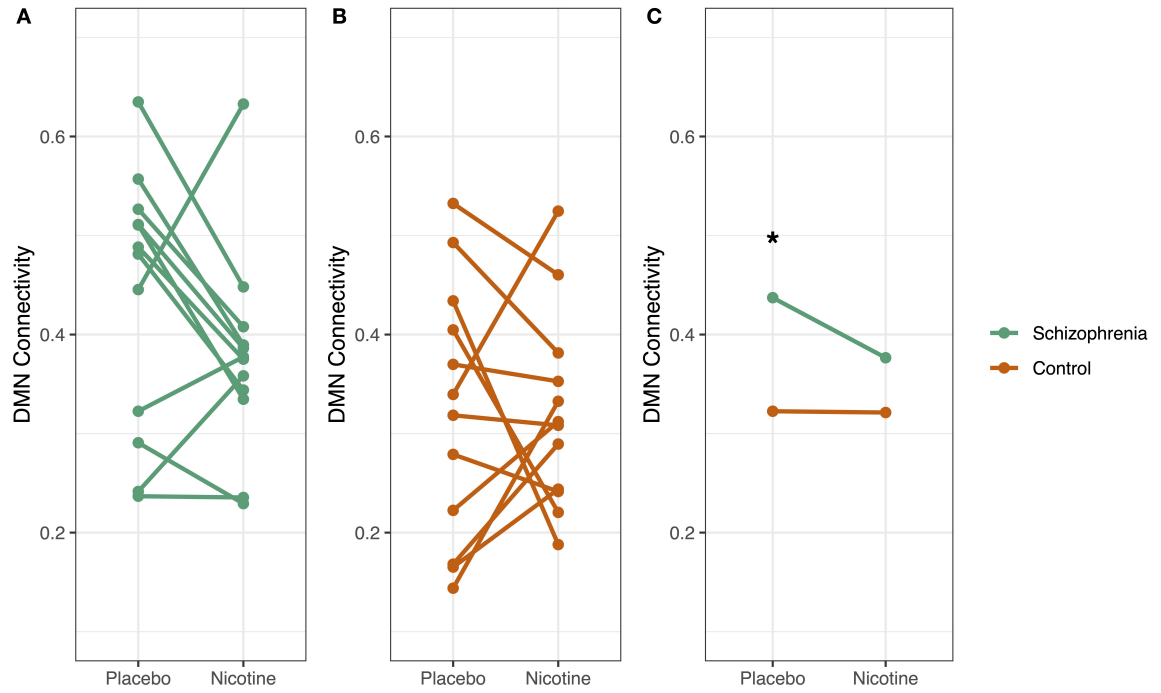

FIGURE 5 | Diagnosis-specific changes in DMN connectivity by drug condition. Whole default mode network (DMN) connectivity for each participant was measured at two timepoints: at placebo and at nicotine administration. In schizophrenia **(A)**, DMN connectivity decreased with nicotine administration, but this pattern was not evident in controls **(B)**. Subjects with schizophrenia had significantly higher DMN connectivity compared to controls in the placebo condition (*$p < 0.05$) but not with nicotine administration **(C)**. There was a trend-level interaction between diagnosis and smoking on DMN connectivity ($p = 0.09$), where smoking and schizophrenia diagnosis both increased DMN connectivity.

drug by diagnosis interaction ($p = 0.09$). Our observation in Cohort 2 that nicotine normalizes DMN hyperconnectivity in schizophrenia was confirmed when we subsequently analyzed DMN connectivity in the initial cohort. We observed that in Cohort 1, there was no difference in DMN connectivity between smokers with schizophrenia and control smokers, suggesting that nicotine may be normalizing connectivity to control levels.

Our results imply a key role of the DMN in nicotine dependence in schizophrenia. Others have previously identified the involvement of the DMN in nicotine dependence in individuals without a co-morbid psychiatric disorder (31, 32, 41–43). However, we observed diagnosis-specific effects of nicotine on the DMN in schizophrenia that were not observed in controls. Notably absent from our data-driven analysis was any significant link between tobacco consumption and salience/reward network connectivity.

However, questions remain: is there a cognitive or behavioral benefit from nicotine's normalization of DMN connectivity? Although our current data is unable to answer this question directly, we hypothesize there is a cognitive benefit from normalized DMN connectivity. Cognitive deficits have been correlated with increased DMN connectivity (44). Nicotine improves attention in schizophrenia (11). Attentional performance is directly related to the ratio of DAN connectivity to DMN connectivity, such that higher DMN connectivity corresponds with worse performance (45). We therefore hypothesize that nicotine use *in schizophrenia* is driven by a need to normalize DMN connectivity and thereby correct attentional deficits (**Figure 6**). We are unable to test this hypothesis using the current data, as no cognitive measures were collected. Another unanswered question is how this altered DMN connectivity occurs. This may occur during development, but additional research studying network connectivity in the prodrome may provide further insights.

Our study has several strengths, notably that we used an agnostic, data-driven approach that was successful in identifying schizophrenia-specific effects. Existing studies of nicotine and schizophrenia have not explained the diagnosis-specific relationships between nicotine and biology. This is the first study to examine individual variation in nicotine use to identify a biological correlate for nicotine dependence in schizophrenia. Our analysis was strengthened by the use of individual variation in nicotine use and continuous variables (cigarettes per day, nicotine dose) rather than categorical comparisons between smokers and non-smokers.

This study uniquely allowed us to probe issues of causality by use of a nicotine intervention in Cohort 2. If two variables are causally linked experimentally, then manipulating one variable should induce change in the other. In Cohort 2, we experimentally manipulated administered nicotine dose and measured network connectivity. We observed that nicotine directly acted upon the DMN, a network which our first analysis

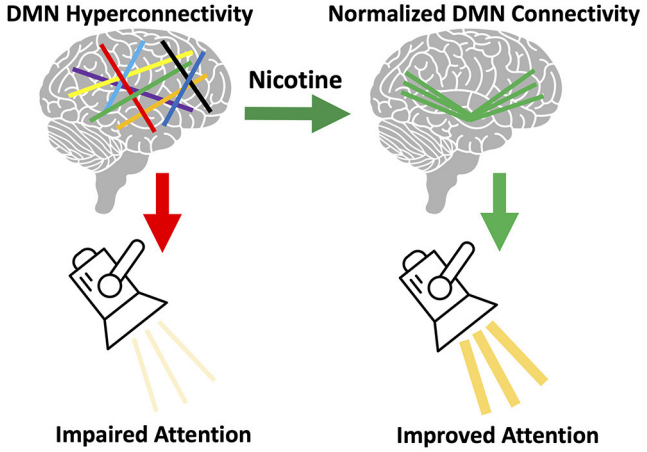

FIGURE 6 | Proposed model of brain circuitry driving nicotine use in schizophrenia. We observed default mode network (DMN) hyperconnectivity in our sample of individuals with schizophrenia, consistent with prior literature (33). We also observed that acute nicotine administration normalized DMN hyperconnectivity in schizophrenia. Based on this data, we hypothesize that individual variation in the magnitude of this DMN disruption gives rise to: (a) variation in the severity of network disorganization and (b) variation in severity of nicotine use. We propose that the DMN mediates the relationship between nicotine use and cognition in schizophrenia. DMN hyperconnectivity is linked to poor attentional performance (45) and, in healthy controls, nicotine can both reduce DMN connectivity and improve attention (11). We propose that DMN connectivity mediates the relationship between nicotine use and attentional performance and that disruption of this network in schizophrenia drives the need for nicotine to correct network pathology (and cognition).

(Cohort 1) linked to nicotine dependence. This allowed us to identify the direction of the relationship between nicotine and DMN hyperconnectivity: that nicotine reduced—and actually normalized—DMN hyperconnectivity in the schizophrenia group. A key strength of this approach was the use of an independent second cohort of a nicotine intervention and measures of within-subjects change which corroborated the results of our data-driven analysis in the first cohort. This complementary combination of studies is rare and powerful, despite the small sample of each cohort individually.

The major limitation of this study is the small sample size, which increases the risk of type I and type II errors. Although the crossover study design in Cohort 2 allows for detection of within-subject drug effects, Cohort 2 was not powered to observe a significant drug x diagnosis interaction. We show significant group-level differences of the DMN with placebo that are no longer significant after nicotine administration. This lack of a difference is attributable to the change in connectivity observed in the schizophrenia population (**Figure 5**), but there are not enough individuals in the group to achieve statistical significance for a drug x diagnosis interaction. Given the heterogeneity of schizophrenia, is also possible that these results may only apply to a subpopulation of people with schizophrenia. Our preliminary results require replication in a larger cohort.

There are several other limitations to our study, including the difference in age between controls and participants with schizophrenia in Cohort 1, although the multivariate pattern analysis controlled for age. Another limitation of the study is the relatively short resting scan sequence used in both cohorts (6.2 min, TR = 3 s). Another limitation of this study is the lack of cognitive measures, which would be important to further elucidate the consequences of nicotine's effects on DMN connectivity.

Our analysis was not powered to detect differences between nicotine-dependent and non-nicotine-dependent populations. The schizophrenia and control groups were imperfectly matched, leading to a disproportionate percentage of nicotine dependent individuals in the schizophrenia group, which could bias the results such that they were experiencing nicotine withdrawal during the placebo condition. However, in a control analysis, we did not observe any significant effects of withdrawal on connectivity, and overall there were low levels of reported withdrawal. While DMN connectivity would be expected to correlate with levels of withdrawal (41), we did not observe this relationship, likely due to the fact that our study was designed to avoid peak withdrawal symptoms, and as a result, participants experienced minimal withdrawal symptoms. It is also possible that we did not observe a correlation between DMN connectivity and withdrawal due to the small sample size. Further, because the administered nicotine dose was related to smoking severity, we are unable to completely isolate an effect of nicotine administration that is independent of severity of nicotine dependence. Group differences could have been influenced by antipsychotic medication. In the future, we call on the large-scale data community to begin to include nicotine use data to enhance the reproducibility of these findings.

The current work identified DMN hyperconnectivity in the schizophrenia group, which was normalized by acute nicotine administration, thus indicating a direct, schizophrenia-specific effect of nicotine on network connectivity. However, the precise cognitive or behavioral consequence of nicotine-induced changes in mitigating DMN hyperconnectivity has not been elucidated. Future studies should relate changes in attentional performance to change in DAN/DMN connectivity pre- and post-nicotine. If network hyperconnectivity is corrected by nicotine, which, in turn, improves cognitive deficits, correcting this network problem may improve cognition. Neuromodulation, such as repetitive transcranial magnetic stimulation, could be one way to correct this network hyperconnectivity and provide a potential treatment for nicotine dependence in this population.

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 Massachusetts General Hospital and McLean

Hospital Institutional Review Boards. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RB, MH, AJ, LM, and HW contributed to conception and design of the study. AB, RB, UN, and HW performed the neuroimaging analysis. HW performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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MINI REVIEW
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Noninvasive Brain Stimulation for Nicotine Dependence in Schizophrenia: A Mini Review

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Individuals with schizophrenia are 10 times more likely to have a tobacco use disorder than the general population. Up to 80% of those with schizophrenia smoke tobacco regularly, a prevalence three-times that of the general population. Despite the striking prevalence of tobacco use in schizophrenia, current treatments are not tailored to the pathophysiology of this population. There is growing support for use of noninvasive brain stimulation (NIBS) to treat substance use disorders (SUDs), particularly for tobacco use in neurotypical smokers. NIBS interventions targeting the dorsolateral prefrontal cortex have been effective for nicotine dependence in control populations—so much so that transcranial magnetic stimulation is now FDA-approved for smoking cessation. However, this has not borne out in the studies using this approach in schizophrenia. We performed a literature search to identify articles using NIBS for the treatment of nicotine dependence in people with schizophrenia, which identified six studies. These studies yielded mixed results. Is it possible that nicotine has a unique effect in schizophrenia that is different than its effect in neurotypical smokers? Individuals with schizophrenia may receive additional benefit from nicotine's pro-cognitive effects than control populations and may use nicotine to improve brain network abnormalities from their illness. Therefore, clinical trials of NIBS interventions should test a schizophrenia-specific target for smoking cessation. We propose a generalized approach whereby schizophrenia-specific brain circuitry related to SUDs is be identified and then targeted with NIBS interventions.

Keywords: schizophrenia, substance use disorder (SUD), nicotine dependence, smoking, noninvasive brain stimulation (NIBS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current simulation, tobacco

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INTRODUCTION

Worldwide, 1.3 billion people use tobacco (1). Individuals with schizophrenia are 10 times more likely to have a tobacco use disorder than the general population (2–4). It is estimated that 64–79% of those with schizophrenia smoke tobacco regularly (5, 6), a prevalence three-times that of the general population. As a result, people with schizophrenia die nearly 30 years earlier from illnesses attributable to tobacco smoking (7).

Noninvasive brain stimulation (NIBS) has been investigated for the treatment of substance use disorders (SUDs), including nicotine dependence. Repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES) are the two most common forms of NIBS being investigated for SUDs. In the application of rTMS, an electromagnetic coil is placed on the scalp. An electrical current is pulsed through this wire coil, which generates a magnetic field that can either increase or decrease neuronal firing beneath the coil. Multiple pulses are delivered at a given frequency, intensity, and duration. These parameters change the neuronal effects of rTMS. High frequency rTMS (e.g., 10-20 Hz) tends to increase neuronal firing, while low frequency rTMS (e.g., 1 Hz) tends to decrease neuronal firing (8).

tES influences brain circuits by producing a weak direct or alternating current through the use of electrodes placed over the scalp. The electrical currents from tES facilitate action potentials, where anodal stimulation enhances cortical excitability and cathodal stimulation diminishes cortical excitability (9–12). Although there are different types of tES, we focus on transcranial direction current stimulation (tDCS), which involves a continuous source of electrical stimulation and is non-frequency dependent (13). In tDCS, a low intensity direct current is applied to the scalp using two or more electrodes. Under the anodal electrode, resting membrane potential decreases, which increases cortical excitability, while under the cathodal electrode, the membrane is hyperpolarized, which decreases excitability (9–11).

NIBS techniques enable targeted intervention on specific brain circuits, including those involved in the development and persistence of SUDs (**Figure 1**). The largest body of evidence supports the use of NIBS for tobacco use, as evidenced by the August 2020 Food and Drug Administration approval of rTMS for smoking cessation (15).

Despite the problem of tobacco use in schizophrenia, there have been very few studies of NIBS in this population. In this Mini-Review, we briefly review the neurobiological evidence supporting NIBS for nicotine dependence in a non-schizophrenia population followed by the existing literature using NIBS for nicotine dependence in schizophrenia. We consider the mixed results of the trials of NIBS for nicotine dependence in schizophrenia and conclude by offering a novel path forward whereby schizophrenia-specific brain circuitry related to SUDs is be identified and then targeted with NIBS interventions.

NIBS for Nicotine Dependence Targets the Dorsolateral Prefrontal Cortex

Multiple studies support the use of rTMS for nicotine dependence in healthy smokers (15–21). Most of these studies have used high frequency 10 Hz rTMS delivered to the left dorsolateral prefrontal cortex (DLPFC) ranging from a 15-min single-session (17) to multi-session experiments (15, 16, 19, 21). High frequency stimulation of the DLPFC has been proposed to activate this region and thereby improve "top-down" regulation of brain regions involved in craving and drug-seeking behavior (22). Moreover, administration of rTMS to the left DLPFC stimulates dopamine release in the striatum (23, 24), anterior cingulate cortex, and medial prefrontal cortex (24).

However, in the Zangen et al. study, which earned rTMS FDA-approval for smoking cessation, high frequency bilateral rTMS was targeted to the lateral prefrontal and insular cortices (15). This study used an H4-coil (Brainsway, Israel), which has been shown in electric field models to bilaterally stimulate neuronal pathways in the lateral prefrontal cortex and insula at an intensity above the neuronal threshold for activation. Targeting of these regions has been proposed to reduce craving in response to smoking cues.

Active rTMS treatment has been associated with decreased cigarette consumption and craving compared to sham (15–17, 19, 21). Moreover, a systematic review and meta-analysis observed that 10 Hz rTMS to the left DLPFC was associated with the greatest reductions in smoking frequency (25).

Despite these promising clinical data, the mechanism of the effects of rTMS on circuits related to nicotine dependence remains largely unknown. Li et al. observed that after 10 sessions of 10 Hz rTMS to the left DLPFC, active TMS inhibited brain activity in the right insula and thalamus and decreased connectivity from the DLPFC to the left medial orbitofrontal cortex, suggesting TMS may reduce reactivity to smoking cues (18).

In addition to rTMS, tDCS has also been shown to impact nicotine dependence. Anodal DLPFC (left and right) tDCS has also demonstrated effectiveness in reducing cue-induced craving and cigarette consumption (26–28). A systematic review and meta-analysis observed that right-anodal, left-cathodal tDCS to the DLPFC significantly reduced cue-induced craving (29). Another study observed that 20 sessions of tDCS over 12 weeks for smoking cessation achieved comparable abstinence rates as 8 weeks of treatment with 300 mg bupropion (30). Despite multiple studies supporting the effects of tDCS on tobacco use, another group observed the effects of tDCS on cigarette craving, cigarette consumption, and executive function were no different from placebo (31).

The mechanism by which tDCS affects craving and cigarette use also remains unknown. Anodal right DLPFC/cathodal left occipital tDCS reduced smoking craving and increased brain reactivity to smoking cues in the right posterior cingulate (32). There is evidence linking the effects of tDCS to the DMN in smokers. Left-anodal DLPFC/right-cathodal vmPFC tDCS increased deactivation of DMN nodes during a working memory task and increased anterior cingulate activity during an error-monitoring task. The effect of tDCS on the DMN was more pronounced when smokers were in a sated (rather than withdrawn) state (33).

NIBS for Nicotine Dependence in Schizophrenia Has Mixed Results

We performed a literature search to identify articles using any form of NIBS for the treatment of nicotine

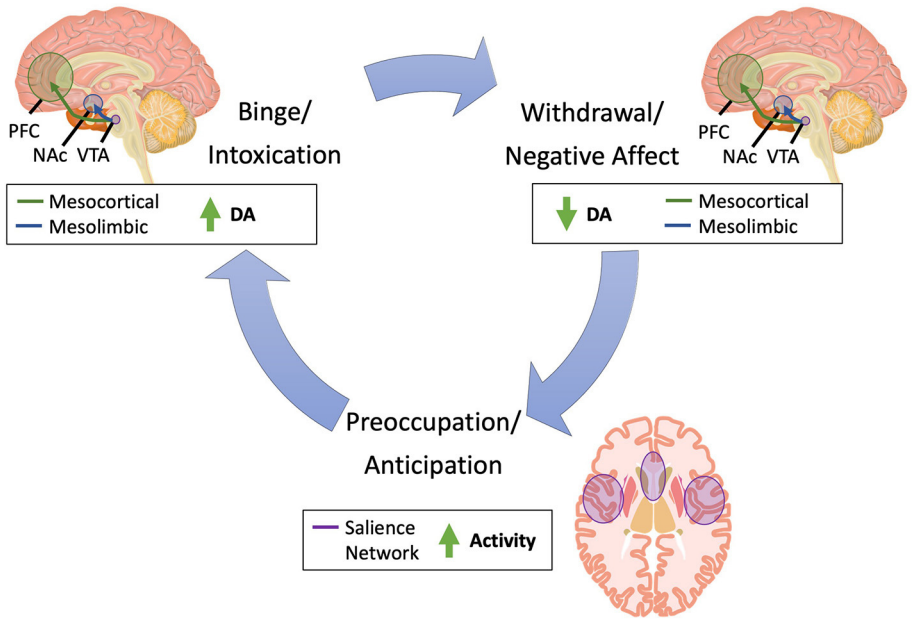

FIGURE 1 | Brain pathways implicated in substance use. Substance use is characterized by three primary phases: (1) binge/intoxication, (2) withdrawal/negative affect, and (3) preoccupation/anticipation (14). In the binge/intoxication phase, substance use leads to acute increases in dopamine in the mesolimbic and mesocortical circuitry, which drives incentive salience and drug-seeking. In the withdrawal/negative affect, dopamine acutely decreases in these same circuits, leading to negative emotional states and dysphoric and stress responses. Finally, in the preoccupation/anticipation phase, increased activity in the salience network, which includes the insula and dorsal anterior cingulate cortex, leads to craving and deficits in executive function. DA, dopamine; NAc, nucleus accumbens; PFC, prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area.

dependence in people with schizophrenia. We searched PubMed using search terms for NIBS (i.e., transcranial electrical stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation), schizophrenia, and nicotine dependence. We excluded any articles that were not primary research studies, including literature reviews, case reports, and meta-analyses.

Studies not meeting inclusion criteria were excluded based on title and abstract. The remaining studies were evaluated based on full-text articles and selected if they met inclusion and exclusion criteria. Following this initial search and screen, we manually searched any relevant systematic reviews and performed a citation analysis to identify any additional articles that met inclusion criteria.

Our initial search identified 21 results. After screening titles and abstracts, 13 full-text manuscripts were evaluated. Seven of these articles were excluded for not studying schizophrenia ($n = 1$), not investigating NIBS as a treatment for nicotine dependence ($n = 3$), and not primary research articles ($n = 3$). We identified six studies of NIBS interventions for nicotine dependence in schizophrenia that met our inclusion and exclusion criteria (**Table 1** and **Supplementary Figure 1**).

The studies were from multiple countries, including Canada ($n = 2$) (34, 38), China ($n = 1$) (36), the Czech Republic ($n = 1$) (35), Germany ($n = 1$) (37), and the United States ($n = 1$) (39).

Of the six studies we identified, there were five studies of rTMS and one study of tDCS. Five studies were randomized, sham-controlled trials. One study involved only open-label treatment. Only two studies observed a decrease in cigarette use while only one study observed decreased cigarette craving. We describe these studies in detail in order to understand the reason for these mixed results.

We identified 5 studies using rTMS for nicotine dependence in schizophrenia (34–38). Wing et al. conducted a 10-week randomized, double-blind, sham-controlled trial of rTMS for smokers with schizophrenia to reduce craving during a smoking cessation attempt (34). Individuals received 4 weeks of rTMS (Weeks 1-4) in addition to weekly group therapy and transdermal nicotine patch (21 mg) (Weeks 3-9). High frequency rTMS (20 Hz) was delivered bilaterally to the DLPFC five times per week for a total of 20 sessions. Fifteen participants were randomized to active stimulation ($n = 6$) or sham stimulation in the single-wing tilt position ($n = 9$). Active treatment with rTMS significantly reduced craving in week 1 but not in weeks 2-4. Notably, rTMS did not increase abstinence rates. Authors suggested that future studies should evaluate rTMS for smoking cessation in the absence of therapy and nicotine patch in a larger study population and after a longer period of abstinence.

In a secondary analysis of the rTMS for the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial, Kamp et al. analyzed the effect of high frequency rTMS on daily cigarette consumption in a sample of individuals with schizophrenia with

TABLE 1 | Comparison of studies using NIBS for nicotine dependence in schizophrenia.

References	TMS/tDCS	*N*	Smoking cessation treatment	Stimulation site	Parameters	Sessions	Sham-controlled?	Craving	Cigarette use
Wing et al. (34)	TMS	15	Nicotine patch (21 mg)	Bilateral DLPFC	20 Hz, 90% RMT, 750 pulses	20	Yes	↓	No change
Prikryl et al. (35)	TMS	35	-	L DLPFC	10 Hz	21	Yes	-	↓
Huang et al. (36)	TMS	37	-	L DLPFC	10 Hz	21	Yes	-	↓
Kamp et al. (37)	TMS	67	-	L DLPFC	10 Hz	15	Yes	-	No change
Kozak et al. (38)	TMS	27	-	Bilateral DLPFC	20 Hz	6	No	No change	-
Smith et al. (39)	tDCS	37	-	Anode L DLPFC; Cathode contralateral supraorbital ridge	2 mA	5	Yes	No change	No change

DLPFC, dorsolateral prefrontal cortex; -, not assessed.

predominantly negative symptoms (37). Participants ($n = 67$) were randomized to active or sham rTMS. Active rTMS (10 Hz) was administered to the left DLPFC five times per week for 3 weeks for a total of 15 sessions. Investigators did not observe a significant effect of time, group, or group × time on daily cigarette consumption.

Kozak et al. also delivered 20 Hz rTMS to the left DLPFC but instead used a crossover study design (38). Participants received twice daily rTMS for 3 days. Individuals were assessed under conditions of nicotine satiety (day 2), following 16 h of acute abstinence (day 3 morning), and upon smoking reinstatement (day 3 afternoon). A total of 27 participants (13 schizophrenia, 14 controls) completed the study. Investigators observed that overnight abstinence produced the expected effects of increasing tobacco craving and withdrawal and impairing cognitive performance. However, active rTMS did not affect this pattern, suggesting that 3 days of rTMS was insufficient to reduce the acute effects of nicotine withdrawal.

Prikryl et al. delivered 10 Hz rTMS or sham to the left DLPFC in 35 male schizophrenia participants for 21 days (35). They observed that cigarette consumption was significantly reduced for the active treatment group after only 1 week of stimulation. This reduction remained statistically significant through the follow-up assessment.

Huang et al. applied 10 Hz rTMS or sham to the left DLPFC in 37 non-treatment-seeking male smokers with schizophrenia for 21 days. Individuals who received active rTMS showed a significant reduction in number of daily cigarettes smoked beginning after the first week of treatment (36). This significant reduction in cigarette use was sustained in the rTMS group compared to the control group through the follow-up assessment 21 days after treatment ended. There were no correlations between reduction in cigarette use and schizophrenia symptoms, depressive symptoms, or performance on the Wisconsin Card Sorting Test.

We identified only one study of tDCS for nicotine use in schizophrenia (39). Smith et al. applied 2 mA tDCS for five sessions to 37 individuals with schizophrenia. They observed the active treatment group had significant improvements in the MATRICS Consensus Cognitive Battery composite score and subscores for working memory and attention-vigilance. However, they did not observe any significant changes in psychiatric symptoms, cigarette consumption, or craving.

In summary, only half of these studies reported a significant effect on cigarette use or craving in schizophrenia. What explains the mixed results when NIBS is applied to the DLPFC in schizophrenia?

Is There an Alternative Network and Cognition-Centric Explanation for the Smoking Prevalence in Schizophrenia?

NIBS targeting the DLPFC has been effective for nicotine dependence in neurotypical smokers—so much so that it is now an FDA-approved treatment for smoking cessation. However, this has not borne out in the studies using this approach in schizophrenia. Is it possible that nicotine has a unique effect in schizophrenia? If that is the case, then perhaps NIBS interventions should instead be tested on a schizophrenia-specific target.

Individuals with schizophrenia may receive additional benefit from nicotine's pro-cognitive effects than control populations. Nicotine improves cognition both in controls and in individuals with schizophrenia (40). Nicotine's pro-cognitive effects are largely due to binding to the alpha7 subunit of the nicotinic acetylcholine receptor (nAChR) in the hippocampus and anterior cingulate (41, 42). In schizophrenia, this leads to improved sensory gating, improved attention (43) and working memory (44), and increased thalamocortical functional connectivity (45). Individuals with schizophrenia have decreased nAChR expression in brain regions that are central to higher cognitive functioning (46). Moreover, following nicotine withdrawal, schizophrenia individuals show greater impairments in attention and executive function than healthy controls (47).

Nicotine's effects on cognition have been linked to reducing the activity and connectivity of the default mode network (DMN). The DMN is active during self-referential thinking (48, 49). Importantly, DMN activity is suppressed when one is engaging in a task, and task performance is dependent upon

successfully suppressing DMN activity. Impaired attention has been linked to DMN hyperconnectivity in healthy controls (50) and schizophrenia (51, 52). Acute nicotine administration in healthy controls decreases DMN activity during an attention task (53) and in the resting state (54). Nicotine suppresses activity in the DMN while withdrawal activates it (55, 56). Moreover, during nicotine withdrawal, the DMN has been observed to be hyperconnected (57). The DMN is activated during exposure to smoking-related cues (58–60).

People with schizophrenia may use nicotine in order to improve brain network abnormalities from their illness. Nicotine's cognitive-enhancing effects have been linked to reduction of DMN activity and hyperconnectivity. Notably, DMN hyperconnectivity is a hallmark of the neurobiology of schizophrenia (61). Therefore, individuals with schizophrenia may be using nicotine as a form of "self-medication" in order to reduce their default mode network hyperconnectivity and thereby improve their cognitive performance. This would imply a schizophrenia-specific brain basis for the pathophysiology of nicotine dependence in this population and would therefore suggest NIBS interventions should use an alternative target in schizophrenia.

DISCUSSION

The prevalence of nicotine dependence in schizophrenia is staggering compared to the general population. Despite the significant decreased life expectancy caused by tobacco use in this population, there are no schizophrenia-specific smoking cessation treatments.

NIBS is being investigated for multiple SUDs, including nicotine dependence. rTMS recently received FDA-approval as a treatment for smoking cessation in neurotypical smokers. We identified 6 studies of NIBS for nicotine dependence in schizophrenia. These studies all stimulated the DLPFC, with the goal of improving "top-down" regulation of brain circuitry involved in reward and response to smoking cues (i.e., salience). However, their results were heterogeneous, suggesting the same target used to treat nicotine dependence in controls may not be effective in schizophrenia.

This suggests there is perhaps an alternative explanation for the etiology of nicotine dependence in schizophrenia. Accordingly, this would also suggest a schizophrenia-specific target should be identified for NIBS interventions.

We would propose that the DMN may be a schizophrenia-specific target for nicotine dependence in schizophrenia. Nicotine has been linked to improved attentional performance, and impaired attentional performance is associated with DMN hyperconnectivity, a finding commonly observed in schizophrenia. Acute nicotine administration reduces this DMN hyperconnectivity. This suggests individuals with schizophrenia may be using nicotine to reduce the hyperconnectivity of their DMN in order to improve cognitive deficits. Therefore, TMS could be used to restore normal connectivity patterns in the DMN, potentially improving cognitive performance and reducing the drive to use nicotine in schizophrenia. In this way, the DMN could offer a schizophrenia-specific target for NIBS smoking cessation treatments. Clinical trials targeting the DMN for smoking cessation in schizophrenia are readily accessible with existing technology and should be conducted. Indeed, previous studies have modulated the DMN by stimulating network nodes in the cerebellum in healthy controls (62) and in schizophrenia (63).

NIBS interventions offer great potential to develop treatments for other co-occurring substance use disorders in schizophrenia. In order to develop such treatments, we must first identify the brain circuit abnormalities unique to co-occurring substance use and schizophrenia, similarly to what we have proposed with nicotine dependence. NIBS interventions can be used to perturb the identified neurocircuitry and measure changes in substance use outcomes (e.g., subjective substance use, biochemical measures of substance use, craving). This process thereby allows for identification of causal relationships between brain circuitry and substance use patterns (64). Then, forms of NIBS can be developed to target these abnormal brain circuits as substance use interventions.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and preparation of the manuscript and approved of 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.2022.824878/full#supplementary-material

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Neuromodulation to Treat Substance Use Disorders in People With Schizophrenia and Other Psychoses: A Systematic Review

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Background: Substance use disorders (SUDs) are a common yet poorly studied comorbidity in individuals with psychotic disorders. The co-occurrence of the two complicates recovery and interferes with pharmacological and behavioral treatment response and adherence. Recently, researchers have been exploring both invasive and non-invasive neuromodulation techniques as potential treatment methods for SUDs. We review the evidence that neuromodulation may reduce substance craving and consumption in individuals with schizophrenia.

Methods: A comprehensive literature search of PubMed, MEDLINE, and PsycINFO databases was conducted ($N = 1,432$). Of these, we identified seven studies examining the effects of repetitive transcranial magnetic stimulation (rTMS) and two studies using transcranial direct current stimulation (tDCS) on drug consumption and craving in schizophrenia or schizoaffective disorders.

Results: Despite the limited number of studies in this area, the evidence suggests that rTMS to the dorsolateral prefrontal cortex (DLPFC) may reduce cannabis and tobacco use in patients with schizophrenia and schizoaffective disorder. Findings with tDCS, however, were inconclusive.

Discussion: Our systematic review suggests that rTMS applied to DLPFC is a safe and promising therapeutic technique for the management of comorbid schizophrenia and SUDs, with the majority of the evidence in tobacco use disorder. However, there was substantial heterogeneity in study methods, underscoring the need to optimize stimulation parameters (e.g., frequency, duration, and target regions). Larger clinical trials are needed to establish the efficacy of rTMS in reducing drug consumption and craving in psychotic patients, ideally in comparison to existing pharmacological and behavioral interventions.

Keywords: substance use disorder, nicotine, cannabis, psychosis, schizophrenia, neuromodulation, rTMS, tDCS

INTRODUCTION

Schizophrenia (SCZ) is a serious mental illness affecting nearly 20 million people worldwide (1). SCZ is characterized by positive (i.e., paranoia and hallucinations), negative (i.e., amotivation and anhedonia), disorganized (i.e., thought disorder and disorganized behaviors), and cognitive (i.e., deficits in attention and sensory processing) symptoms (2). The course and prognosis of SCZ is often complicated by co-occurring substance use disorders (SUD), evidenced by a global prevalence of ∼42% for any SUD, including illicit drugs (27.5%), cannabis (26.2%), and alcohol [24.3%; (3)]. Such high levels of comorbidity are potentially due to, inter alia, shared genetic and environmental factors increasing SUD vulnerability [for review see (4, 5)] or to alleviate cognitive and psychotic symptoms (6). Use of psychoactive substances can interfere with antipsychotic medication (7), are associated with reduced adherence to SCZ interventions (8), and can lead to symptom exacerbation (9). There are mixed findings with respect to antipsychotics for treating SUDs in SCZ and preliminary support for the use of naltrexone in reducing alcohol use in SCZ (10). Behavioral interventions have also shown some success in reducing substance use, mostly during the intervention period (10). However, research remains relatively limited as individuals with co-occurring serious mental illnesses are often excluded from SUD clinical trials. Moreover, these methods are difficult to implement in SCZ patients; psychotic symptoms and cognitive deficits may reduce patients' ability to engage meaningfully in SUD behavioral interventions (11), while certain pharmacological addiction interventions may worsen positive symptoms of psychosis (12–14), urging investigation into novel and effective interventions for SCZ patients.

Invasive and non-invasive neurostimulation techniques are emerging innovative treatments that have been investigated in the context of treatment-resistant illnesses (15) in individuals who struggle with adherence. As such, they are a promising modality for treating SUDs in SCZ as they can directly target putative brain regions, such as the prefrontal cortex and nucleus accumbens, that are associated with SCZ and SUD pathophysiology (4) with less effort than is required for medication compliance. Moreover, they are safe, time-effective, and patient-friendly, offering a neuroscience-based treatment that may be superior to conventional medications and behavioral therapies. Such techniques include non-invasive repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), or invasive deep brain stimulation (DBS). The purpose of this review is to systematically review the evidence that neurostimulation techniques reduce substance craving and consumption in individuals with SCZ.

Neurostimulation Methods

Repetitive Transcranial Magnetic Stimulation

rTMS is a non-invasive stimulation method that involves positioning an electromagnetic Figure-of-8 or H-coil on the scalp to produce a time-varying magnetic field (16, 17). This current can be localized to specific brain regions to modulate neurotransmission (18). Options include low- or high-frequency rTMS, which tend to produce inhibitory or excitatory effects, respectively (17). A variation of rTMS is intermittent or continuous theta burst stimulation, which generally produces similar results, usually with shorter session duration (19, 20). rTMS is well tolerated, with some people reporting headache, tingling, or lightheadedness (20–22) and rarely cognitive deficits or seizures [0.071%; (23, 24)], with H-coil carrying a slightly higher risk than Figure-of-8.

Transcranial Direct Current Stimulation

tDCS is another non-invasive stimulation method that involves a low-intensity, steady-state direct current that is delivered to a localized brain region via two or more electrodes on the scalp (18, 25). There are variations between protocols regarding the size and number of electrodes, duration of stimulation, and current strength that modify the dispersion of the current to the brain. tDCS electrodes can either increase (if anodal) or decrease (if cathodal) the likelihood of neuronal firing by modulating the resting membrane potential (25). Furthermore, prolonged stimulation may modify synaptic plasticity via long-term potentiation or depression (17, 25). tDCS is relatively low risk, with some patients reporting sleepiness, minor discomfort, or mild burning or pain in the neck or scalp (26).

Deep Brain Stimulation

DBS is an invasive technique, where microelectrodes are embedded in the brain, thus allowing for sustained modulation of neuronal firing to regulate neurotransmission in specific brain regions (18). Embedded electrodes are coupled with a pulse generator to facilitate continuous stimulation (18). Although DBS offers a more localized and deeper signal that can modulate oscillatory activity, it involves a surgical procedure and thus carries risks including infection or hemorrhage (27).

Evidence for Neurostimulation in Substance Use Disorders

The evidence to date suggests that stimulation of regions in the mesocorticolimbic system may modulate dysregulated neurotransmitter release, thus reducing craving and consumption of addictive substances (16, 28). The most consistent positive results occur when multiple sessions of high-frequency (>10 Hz) stimulation is applied to the dorsolateral prefrontal cortex (DLPFC), as this enhances its inhibitory actions on the mesolimbic DA circuits (16, 18, 28). Indeed, preliminary studies using small sample sizes have found that after 10- 20 sessions, both Figure-of-8 and H-coil rTMS are effective at reducing alcohol cravings (29–32) and consumption (33). Furthermore, figure-of-8 coil rTMS has been effective in reducing cigarette craving and consumption (34–37), cocaine craving (38, 39) and producing greater abstinence rates (40, 41) when applied to the DLPFC. tDCS has also shown promising results in reducing craving and consumption of alcohol, opioids, cannabis, cocaine, and methamphetamines [for review see (18)], and tobacco (42). Additionally, several case series investigating DBS targeting the nucleus accumbens suggest it may also be effective in reducing alcohol craving and intake as well as cocaine use [for review see (17)].

However, there are some studies that are inconsistent with the above findings (43–45). Such discrepancies are likely to due to inconsistencies in stimulation parameters, such as number of pulses, duration of stimulation, stimulation frequency, and number of sessions. These parameters influence whether stimulation is excitatory, the magnitude of the electric field delivered, neuronal activation, and tolerability (23). As such, investigation into the effectiveness of neurostimulation in treating SUDs is paramount, as is standardization of stimulation parameters and extension of this research to individuals with comorbid SCZ and SUDs.

Neurostimulation in Comorbid Schizophrenia and Substance Use Disorders

Given the high prevalence of SUDs (3) coupled with the lack of effective treatments for addiction in SCZ patients, novel, low-effort, and quick to administer treatments are needed. The neuropathological correlates of SCZ, including dysregulated dopaminergic, serotonergic, and cholinergic systems result in characteristic psychopathological symptoms, along with deficits in reward processing and cognitive function (46). Dysregulated responses to rewarding stimuli are thought to underlie the increased reinforcement of substances in SCZ relative to non-psychiatric controls [for review see (5)]. Moreover, individuals with SCZ may use substances as a way to cope with negative symptoms (e.g., restricted affect) and/or attenuate cognitive deficits (9, 47). In light of the promising effects of neurostimulation on regulation of neurotransmitters (28), improvements on negative symptoms in SCZ (48) that may contribute to use, improvements on depressive symptoms (49), cognitive functioning, and reductions in cravings and consumption (17, 18) in non-psychiatric SUDs, individuals with SCZ stand to benefit from investigation into the utility of neurostimulation.

Accordingly, we review the available evidence on neurostimulation techniques as a treatment modality for SUDs in SCZ. In an effort to be comprehensive, all psychotic-spectrum disorders were included in the search, however, only studies assessing SCZ and schizoaffective disorder (SCA) were found.

METHODS

Search Strategy

A comprehensive literature search was conducted by two of the authors (SJ and MS) using PsycINFO, PubMed, and MEDLINE following PRISMA guidelines. Search terms included: neuromodulation, neurostimulation, stimulation, (repetitive) transcranial magnetic stimulation, transcranial direct current stimulation, theta burst stimulation, deep brain stimulation, vagus nerve stimulation, and psychosis, schizophrenia, schizoaffective disorder, schizotypal, delusional, schizophreniform, psychotic, bipolar psychosis, depressive psychosis, and substance use disorder, substances, addiction, drugs, cocaine, crack, cannabis, tobacco, nicotine, alcohol, methamphetamines, amphetamines, opioids. We included only randomized sham-controlled trials (RCT), open-label studies, or case studies whose population had a psychosis-spectrum disorder and whose primary or secondary outcomes were an end point measure of substance consumption or craving. Exclusion criteria included substance-induced psychosis, non-validated measures of substance use, and reviews or meta-analyses.

Risk of Bias

Risk of bias was evaluated using the Cochrane Collaboration Tool (50), which assesses studies on the following criteria: random sequence generation, allocation concealment, blinding of participants and research personnel, blinding of outcome measures, incomplete outcome data, and selective reporting of results.

RESULTS

Study Characteristics

As depicted in **Figure 1**, after identifying 1,438 unique studies, 47 studies were assessed for full eligibility, leaving eight published papers and one unpublished manuscript (rTMS = 7, $n = 204$; tDCS = 2, $n = 49$). Seven of the included studies were RCTs whereas the other two employed an open-label design. All but one of the studies examined the effects of neurostimulation on cigarette craving or consumption in individuals with SCZ or SCA. The remaining study investigated cannabis craving and consumption along with cigarette consumption in SCZ. The main characteristics of the included studies are described in **Table 1** below.

Risk of Bias Assessment

Table 1 shows the results of the risk of bias assessments. Overall, the seven RCTs were of high methodological quality with all but one scoring a 6, while the two open-label studies indicated a high risk of bias.

RTMS Studies

Craving

As seen in **Table 2**, two studies (55, 60) investigated the effects of rTMS on cigarette cravings, measured by the Tiffany Questionnaire for Smoking Urges (TQSU). While both studies administered rTMS at 20 Hz to the DLPFC bilaterally, the short-term (6 sessions; 3 days) study found no reduction in cigarette cravings or withdrawal (55) at the end of stimulation, whereas the longer intervention (20 sessions; 28 days) found a significant reduction in desire and intention to smoke cigarettes in the active group relative to the sham group (60). However, only the acute trial involved contingent abstinence, potentially resulting in increased cravings for participants, making direct comparison difficult. One study investigated the effect of rTMS on the bilateral DLPFC (20 Hz, 20 sessions) on cannabis cravings and withdrawal (56). While not statistically significant, the active group reported greater (50%) reductions in cravings than the sham group, particularly in terms of expectations of positive outcomes (e.g., feeling more social) after using cannabis.

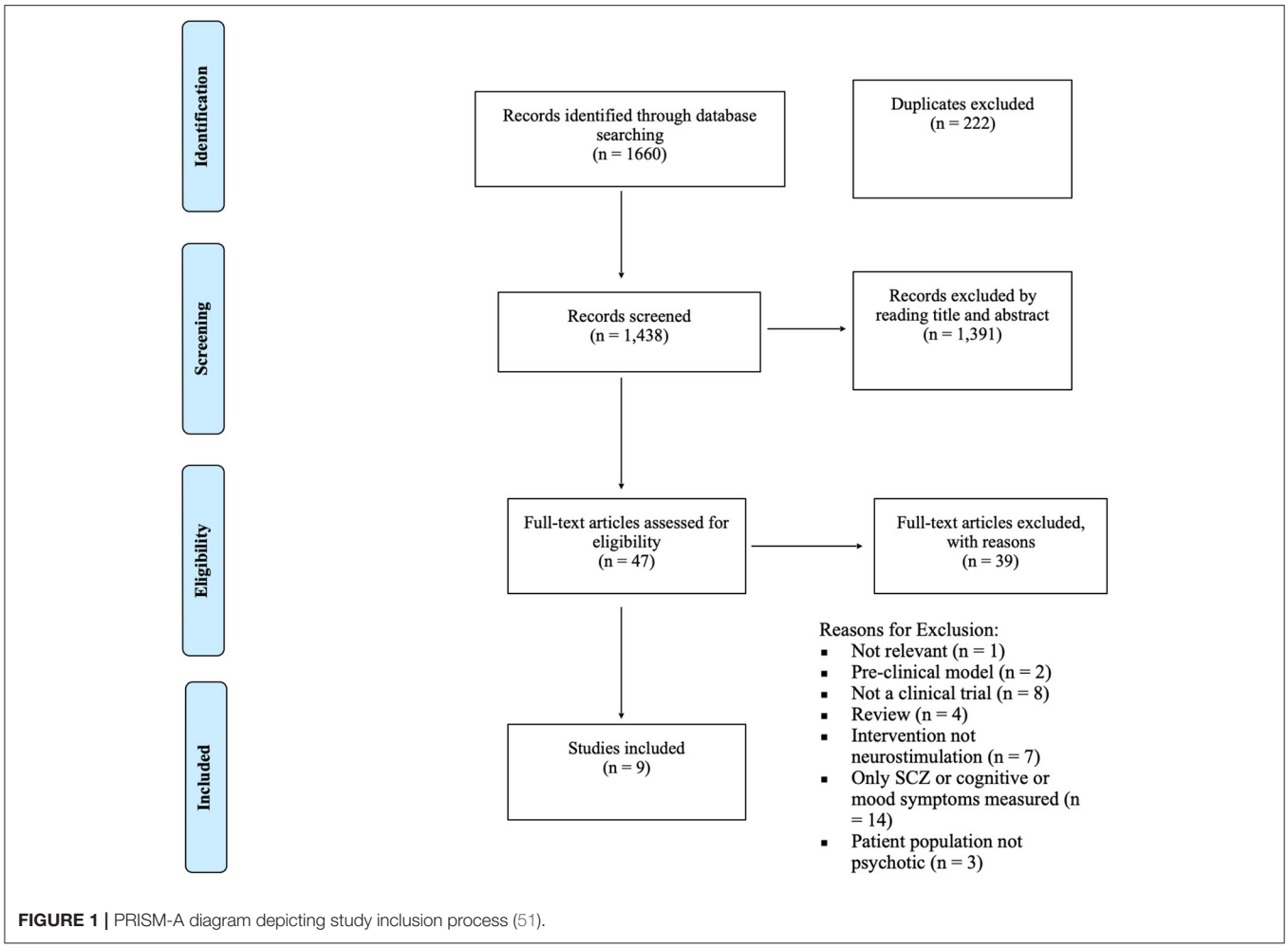

FIGURE 1 | PRISM-A diagram depicting study inclusion process (51).

TABLE 1 | Outcomes of cochrane risk of bias assessment.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Brunelin et al. (52)	!	!	-	-	+	+
Huang et al. (53)	+	+	+	+	+	+
Kamp et al. (54)	+	+	!	+	+	+
Kozak et al. (55)	+	+	+	+	+	+
Kozak-Bidzinski et al. (56)	+	+	+	+	+	+
Prikryl et al. (57)	!	!	-	-	!	!
Prikryl et al. (58)	+	+	+	+	+	+
Smith et al. (59)	+	+	+	+	+	+
Wing et al. (60)	+	+	+	+	+	+

Green, Low risk of bias; Yellow, Medium risk of bias; Red, High risk of bias.

Consumption

Five of the identified studies investigated the effects of rTMS on cigarette or cannabis consumption. Four of these studies applied 10 Hz (15-20 sessions) to the left DLPFC and assessed changes in cigarette consumption from baseline to the 21st day of stimulation (57) or after a 21 day follow-up (53, 54, 58).

TABLE 2 | Main findings from repetitive transcranial magnetic stimulation studies.

References	Study design	Sample	Stimulation target	Stimulation frequency (Hz)	Number of sessions	Primary SUD outcome (effect size)	Secondary outcomes (effect size)	summary of relevant results
Huang et al. (53)	Randomized, double blind, parallel, sham-controlled Active = figure-8 Sham = identical coil shape produces sound but no stimulation	SCZ ($n = 37$, active = 19), M/F = 37/0	Left DLPFC	10	21	Tobacco use disorder; cigarettes smoked from baseline to 21 day follow up (active $d = 2.06$, $p < 0.05$; control $d = 0.2$, $p = 0.18$; difference $f = 0.98$, $p < 0.001$)	PANSS, Wisconsin Card Sorting Test, MADRS (ns)	Active group showed a statistically significant reduction in number of cigarettes smoked compared to control group. No statistically significant differences in secondary measures after treatment, smoking not related to secondary measures.
Kamp et al. (54)	Double blind, randomized, parallel, sham-controlled Active = figure-8, Sham = distortion of coil 45° away from skull	SCZ ($n = 67$, active = 32), M/F = 55/12	Left DLPFC	10	15	Tobacco use disorder; cigarettes smoked from baseline to 21 day follow up ($f = 0.08$, $p = 0.54$). Correlation between number of cigarettes smoked and reduction ($r_{23} = 0.385$, $p = 0.057$)	Covariates: PANSS positive symptoms, gender, mood stabilizers, benzodiazepines (ns), antidepressants ($f = 0.42$, $p < 0.01$)	rTMS did not significantly reduce the number of cigarettes smoked. Higher number of cigarettes smoked tended to predict a greater reduction.
Kozak et al. (55)	Counter-balanced, double blind, cross-over Active = figure-8 Sham = single wing tilt	SCZ ($n = 13$) HC ($n = 14$),	Bilateral DLPFC	20	6	Tobacco use disorder; MNWS, TQSU: time x diagnosis x rTMS (ns)	SDR (ns), HVLT discrimination, time x rTMS ($f = 0.45$, $p = 0.016$)	Acute administration of rTMS did not reduce abstinence-induced cravings or withdrawal.
Kozak-Bidzinski et al. (56)	Randomized, double blind, parallel, sham-controlled	SCZ ($n = 19$, active = 9), M/F = 18/1	Bilateral DLPFC	20	20	Cannabis use disorder; baseline to 28 day follow up; change across groups Grams/day ($d = 0.72$, $p = 0.21$), NarcoCheck ($d = 0.55$, $p = 0.26$), MCQ ($d = 0.49$, $p = 0.19$) MWC ($d = -0.22$, $p = 0.58$) Tobacco use disorder; cigarettes/day ($d = 0.96$, $p = 0.01$)	PANSS total (d = 0.79, $p = 0.02$), CDSS (ns), HVLT, SDR, BART, TMT, digit span, TOL, KDDT, MMN (ns) CPT hit reaction time ($d = 0.17$, $p = 0.048$), variability ($d = 1.64$, $p = 0.04$).	rTMS produced greater reductions of medium magnitude in self-reported and urinalysis cannabis use and cigarettes smoked. Greater reductions in appetitive states of cannabis craving in active group.
Prikryl et al. (57)	Open-label Figure-8	SCZ ($n = 18$), M/F = 18/0	Left DLPFC	10	15	Tobacco use disorder; baseline to 21st day of stimulation; cigarettes/day ($d = 0.69$, $p < 0.01$)	PANSS total ($d = 1.5$, $p < 0.01$) MADRS ($d = 2.1$, $p < 0.01$)	rTMS significantly reduced the number of cigarettes smoked per day during the stimulation period.

(Continued)

TABLE 2 | Continued

References	Study design	Sample	Stimulation target	Stimulation frequency (Hz)	Number of sessions	Primary SUD outcome (effect size)	Secondary outcomes (effect size)	summary of relevant results
Prikryl et al. (58)	Double blind, randomized, parallel, sham-controlled Active = figure-8 Sham = identical coil shape produces sound but no stimulation	SCZ or SCA (n = 35, active = 18), M/F = 35/0	Left DLPFC	10	21	Tobacco use disorder; cigarettes smoked from baseline to 21 day follow up (active, $d = 0.67$, $p < 0.01$; control, $d = -0.03$, $p = 0.59$)	PANSS, MADRS, CDSS (ns)	rTMS significantly reduced the number of cigarettes smoked in the active group with no change in the control group. Other psychopathology symptoms not related to changes in smoking.
Wing et al. (60)	Counter-balanced, randomized, double blind, parallel, sham-controlled Active = figure-8 Sham = single wing tilt	SCZ or SCA (n = 15, active = 6),	Bilateral DLPFC	20	20	Tobacco use disorder; cravings (TQSU; $p < 0.05$), abstinence (ns)	N/A	rTMS significantly reduced desire and intention to smoke in the active group relative to sham group. There was no effect of rTMS on abstinence.

ns, not significant, statistics not reported.
TQSU, Tiffany Questionnaire on Smoking Urges; MCQ, Marijuana Craving Questionnaire; MNWS, Minnesota Nicotine Withdrawal Scale; MWC, Marijuana Withdrawal Checklist; PANSS, Positive and Negative Syndrome Scale; MDRS, Montgomery Asberg Depression Rating Scale; HVLT, Hopkins Verbal Learning Test; CDSS, Calgary Depression Scale for Schizophrenia; CPT, Continuous Performance Test; TMT, Trail Making Test; BART, Balloon Analog Risk Task; TOL, Tower of London Task; KDDT, Kirby Delay Discounting Test; MMN, Auditory Mismatch Negativity; MCCB, MATRICS Consensus Cognitive Battery.

In three of the four studies, rTMS significantly reduced the number of cigarettes smoked relative to the control group; one study did not find a significant reduction (54). However, Kamp et al. found that individuals in the active group who smoked a higher number of cigarettes reported a greater reduction in consumption (54). One study investigating the effects of bilateral DLPFC (20 Hz, 20 sessions) found trending reductions in self-reported and biologically verified cannabis use in the active group that were greater than the sham group, as well as a statistically significant and strong reductions in cigarette use (56).

TDCS Studies

Craving

Table 3 depicts the results of the tDCS studies. One study investigated the effect of tDCS on cigarette cravings. Smith et al. (59) applied 2 mA through a cathode to the contralateral supraorbital ridge and through an anode to the left DLPFC (20 min; five sessions) and found no reduction in urge to smoke or dependence, as measured by the Questionnaire on Smoking Urges.

Consumption

Two studies investigated the effects of tDCS on cigarette consumption. Brunelin et al. (52) applied 2 mA through a cathode to the left temporo-parietal junction and through an anode to the left prefrontal region for 20 min (10 sessions) and found no effect on cigarette consumption. Moreover, cigarette consumption was associated with a reduction in the clinical efficacy of tDCS on auditory hallucinations. However, there was no sham group in this study. Similarly, when applying 2 mA for 20 min (five sessions), through a cathode to the contralateral supraorbital ridge and through an anode to the left DLPFC, Smith et al. (59) found no reductions in self-reported or biologically verified cigarette abstinence.

Secondary Analyses

In three out of the four studies that examined cognitive outcomes, tDCS and rTMS were both effective in improving performance on some measures, including the discrimination index on the Hopkins Verbal Learning Test [HVLT; assesses immediate and delayed recall; (55)], hit reaction time and variability on the Continuous Performance Test [CPT; (56)], and the composite score of the MATRICS Consensus Cognitive Battery (assesses a range of cognitive functioning in SCZ) as well as working memory and attention subscales (59). However, there were a few cognitive tasks on which rTMS had no effect depicted in **Table 2**. With respect to clinical outcomes, two studies found reductions in total scores of the Positive and Negative Symptom Scale (56, 57) and one found improvements on the Montgomery-Asberg Depression Rating Scale (MADRS) as a result of rTMS. Moreover, one study found improvements on auditory hallucinations after tDCS (52). However, three studies found no effects of rTMS ($n = 2$) on the MADRS or PANSS (53, 58) or tDCS ($n = 1$) on PANSS scores or hallucinations (59).

TABLE 3 | Main findings from transcranial direct current stimulation studies.

References	Study design	Sample	Stimulation site	Stimulation density	Stimulation duration	Number of sessions	Anode/ cathode	Primary SUD outcome (effect size)	Secondary outcomes (effect size)	Summary of relevant results
Brunelin et al. (52)	Open-label proof of concept	SCZ (n = 16), M/F = 6/10	Left temporo-parietal junction Left prefrontal region	2 mA	20 min	10	Cathode Anode	Tobacco use disorder, cigarettes smoked (ns)	Auditory hallucination rating scale (d = 0.9, p = 0.005)	No effect of tDCS was observed on cigarette consumption. Smoking status reduced clinical efficacy of tDCS on hallucinations.
Smith et al. (59)	Randomized, double blind, parallel, sham-controlled Sham = 2 mA lasting only 40s, electrodes in place for 20 min	SCZ or SCA (n = 33, active = 17), M/F = 24/9	Contralateral supraorbital ridge	2 mA	20 minutes	5	Cathode Anode	Tobacco use disorder, cigarettes smoked, breathalyzer CO2 levels, QSU (ns)	PANSS, Haddock Hallucination Scale (ns). MCCB (d = 1.03, p < 0.01)	tDCS did not reduce urge to smoke or cigarette dependence nor did it improve abstinence or psychopathology. tDCS did improve cognitive performance.

ns, not significant, statistics not reported.
PANSS, Positive and Negative Syndrome Scale; MCCB, MATRICS Consensus Cognitive Battery.

Adverse Events

rTMS and tDCS procedures were well-tolerated in the included studies. Some participants reported mild to moderate application site pain, neck pain, headache, or dizziness. All resolved naturally (52, 53, 56, 59, 60). No participants dropped out of the study due to pain from the study device. There were no reports of treatment emergent memory or other cognitive deficits, or seizures.

DISCUSSION

Our review of the extant literature suggests that rTMS applied to the left or bilateral DLPFC may be effective in reducing craving for and consumption of tobacco and cannabis in individuals with SCZ or SCA. However, evidence did not support the efficacy of tDCS in reducing cigarette craving or consumption, possibly due to the limited number of stimulation sessions employed (5–10) relative to the rTMS studies where 15 or more sessions were performed. While the results of studies in this review provide support for continuing investigation of rTMS as an addiction treatment, there remains a need for more robust clinical trials as well as standardization of stimulation parameters.

Based on calculated effect sizes (**Tables 2**, **3**) the evidence suggests that 10 Hz of rTMS directed at the left DLPFC for at least 20 sessions is effective in reducing cigarettes smoked per day. Moreover, 20 Hz for at least 20 sessions directed at the bilateral DLPFC is effective in reducing cravings for cigarettes, cigarettes smoked per day, and- albeit on the basis of a single study might be effective in reducing cannabis use. Interestingly, high-frequency rTMS (10 Hz or more) applied to the DLPFC for a greater number of sessions is also supported by data from neurostimulation studies in non-psychiatric SUD samples (18, 28). While difficult to compare across diagnoses, the lack of efficacy of tDCS on tobacco craving and consumption does not align with literature in non-psychiatric individuals with SUDs, which did show significant effects after 1-5 sessions (18) with a similar intensity (2 mA) and duration (20 min). It is possible that neurobiological underpinnings of SCZ are not concordant with tDCS stimulation targets or that more sessions are needed to see similar effects. Further investigation is needed for conclusive guidance.

Although the effectiveness of rTMS in reducing tobacco cravings in people with SCZ was variable across reviewed studies, the null findings in Kozak et al. (55) might be explained by the short number of treatment sessions or by the effects of contingent abstinence. While measurement of cravings is clinically useful and may point to mechanisms through which neurostimulation works (e.g., regulation of reward pathways), they represent subjective ratings of an introspective phenomenon (61) and therefore are subject to bias.

Unverified self-reported changes in consumption were present in five of the reviewed studies. Although this is more informative regarding effectiveness, biologically-verified measures of consumption represent a more objective measure of changes in substance use and should be employed in

future investigations. Moreover, immediately before and after stimulation, fMRI and EEG measures of addiction-related circuitries would be helpful in assessing changes produced through stimulation (62).

Cognitive outcomes were reported in four of the reviewed studies. Improvements were found in three, which may be explained through direct effects of stimulation on targeted brain regions (e.g., DLPFC) mediating cognitive performance or indirectly through reduced substance use. Of note, previous studies have found support for nicotine-induced improvements in SCZ cognitive impairments, specifically in attention, visuospatial working memory, and verbal learning and memory; it has been proposed that these factors may contribute to increased tobacco addiction vulnerability in people with SCZ (47, 63–66). It is also possible that alleviation of clinical symptoms as a direct result of the neuromodulation or an indirect result of reduced substance use may have contributed to improvements in cognitive functioning due to reduced cognitive load or enhancement of cognitive resources. While conclusions are limited due to the preliminary nature of the evidence, future research should investigate whether neuromodulation interventions in prodromal SCZ aimed at improving cognitive deficits are effective in reducing the likelihood of future tobacco or cannabis use disorder.

Evidence of alleviation of depression or positive and negative SCZ symptoms was mixed. However, given that neuromodulation has also been used to ameliorate positive and negative symptoms (67, 68) and meta-analyses have shown rTMS to be effective in the treatment of both major depression and schizophrenia (69). Thus, future studies should continue to investigate the possibility of neuromodulation as an integrated treatment, as well as potential pathways to efficacy via reductions in negative symptoms, while controlling for symptom changes that are associated with reductions in substance use.

While this review shows preliminary support for the use of neuromodulation in individuals with SCZ and SCA, there remains a gap in evidence supporting its use in other psychotic disorders (e.g., bipolar disorder with psychotic features, first-episode psychosis). To that end, there remains a question of who the appropriate candidate for brain stimulation is; would individuals with acute substance-related exogenous psychosis (70) or first-episode psychosis (71) benefit from neuromodulation or should it be reserved for individuals experiencing more chronic and resistant psychosis? Additionally, case-studies (72–74) of rTMS in individuals with mood disorders have reported the occurrence of neuromdulation-induced mania as an adverse event, which is particularly relevant to treating SUDs in individuals with bipolar or depressive disorders with psychotic features. It is emphasized that caution should be exercised and that further empirical research should be conducted to establish definitive guidelines for clinicians.

Limitations

There are a number of limitations to the current review. Primarily, is that despite the high prevalence of cannabis, stimulant, alcohol, and polysubstance use in SCZ and other psychotic-spectrum disorders (75–77), gaps remain in elucidating the effectiveness of neurostimulation for these substances, with only one study investigating cannabis in this population to date (56). Future studies of neuromodulation in SCZ should examine these substances for a more comprehensive understanding of its utility in treating SUDs. Furthermore, despite similar patient samples and outcome measures across studies, the stimulation parameters and targeted brain regions were highly heterogenous. In addition, self-reported substance use is subject to recall bias (78). Future studies should aim to biologically verify reductions in self-reported substance use. Moreover, antipsychotic medications that antagonize D2 dopamine receptors are known to reduce the effectiveness of tDCS on psychopathological symptoms (79), and this was not factored into the included studies. Participants in Smith et al. (59) and Brunelin et al. (52) were on clozapine during stimulation treatment, potentially impacting results. There were no studies of DBS in psychosis-spectrum populations, however, the feasibility of recruiting such patients for invasive brain stimulation procedures may prove challenging. Finally, the majority of the studies were conducted with predominantly male samples. While this may in part be due to sex differences in the diagnosis of SCZ (80) it limits generalizability of these results to females with SCZ.

CONCLUSIONS AND FUTURE DIRECTIONS

rTMS is a promising and well-tolerated option in the treatment of tobacco, and possibly, cannabis use disorders in SCZ and SCA. However, there is a need to optimize stimulation parameters (e.g., frequency, duration, and stimulation target regions), as has been noted in previous reviews (18). In addition, while this review suggests 5-10 sessions of tDCS may not be effective for reducing tobacco use in SCZ, future research should investigate whether more sessions may have efficacy. Larger sham-controlled clinical trials with longer follow-ups and more accurate substance use measures are needed to establish the efficacy of neuromodulation in reducing drug consumption, ideally in comparison to existing pharmacological and behavioral interventions. Moreover, future research should investigate the effects of rTMS on consumption of alcohol and other drugs (e.g., cannabis, cocaine, methamphetamine, opioids) in SCZ and other psychosis-spectrum illness.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

SJ wrote the manuscript. SJ, MS, and NA-S conducted the systematic review. VS, GP, MS, DL,

DC, and TG edited and revised the manuscript. TG, DC, SJ, and MS conceptualized the review. All authors contributed to the article and approved the submitted version.

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Lifetime Cannabis Use Is Not Associated With Negative Beliefs About Medication in Patients With First Treatment Psychosis

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Objective: Cannabis use is common among patients with psychosis, and along with negative beliefs about medication, it has been found to predict poor adherence to antipsychotic drug treatment. Such lack of adherence to antipsychotic drug treatment increases the risk of poor clinical outcomes and relapse in patients with first treatment for psychosis (FTP). However, to date, it is unclear whether cannabis use may be related to negative perceptions about antipsychotic drug treatment.

Methods: A cross-sectional sample of 265 FTP patients with schizophrenia spectrum disorder underwent extensive clinical assessments. Three measures of cannabis use were obtained: lifetime, current and meeting diagnostic criteria for abuse or addiction. For the primary analyses we focused on lifetime cannabis use. The Beliefs about Medication Questionnaire (BMQ) was employed to assess the patients' specific concerns and perceptions of antipsychotic medications, as well as general beliefs about pharmacotherapy. The relationship between lifetime cannabis use and BMQ scores was investigated with general linear model (GLM) analyses, controlling for age and sex.

Results: Patients with lifetime use of cannabis $\geq$10 times were more likely to be male, younger at the age of onset of psychosis and with higher levels of alcohol use and daily tobacco smoking, as compared to the non-users ($p < 0.05$). Neither lifetime use of cannabis, current use nor a cannabis abuse diagnosis was associated with negative beliefs about medicines as measured by the BMQ questionnaire.

Conclusion: Use of cannabis is not linked to negative perceptions about antipsychotic medicines in patients with FTP. Other reasons for poor compliance to antipsychotic drug treatment in cannabis users need to be further investigated.

Keywords: psychosis, schizophrenia, cannabis, substance abuse, BMQ

INTRODUCTION

People with schizophrenia have high comorbidity of substance use disorders (1), in particular cannabis use disorder (2, 3). In patients coming to their first treatment for psychosis (FTP), lifetime exposure to cannabis has been estimated to be up to 80% and current use in at-risk subjects estimated to be 30–40% (4, 5). Cannabis use has been associated with an earlier onset of psychosis, more severe course of the illness, stronger impairment of global functioning, and a higher risk of relapse (4, 6–11). While some authors interpret the increased cannabis use in schizophrenia as a means of self-medication to alleviate psychotic symptoms (12), recent findings indicate that cannabis use also may be a causal factor in developing schizophrenia (13–17) predating the onset of prodromal symptoms (13, 18–20).

Antipsychotic drugs are central to the treatment of severe mental disorders, but it is often difficult to encourage patients to stay on these medications over time. Up to two-thirds of patients with schizophrenia comply poorly to prescribed antipsychotic treatments (21), with increased risks of relapse, hospitalization, and suicide (22). Cannabis use, poor insight and negative beliefs about medication have been found to be significant predictors of poorer compliance in this patient group (23–27). In a previous study of FTP patients, a link between negative attitude and beliefs about medication and adherence to antipsychotic drug treatment was demonstrated (28). Given that cannabis use also has been found to predict poor compliance to antipsychotic drug treatment (23), it is of interest to explore if cannabis use is associated with negative beliefs about medicines. However, to date, no such relationship has been systematically explored. This question is particularly relevant to study in FTP patients because cannabis use may be a modifiable risk factor for treatment non-adherence, while negative attitudes toward medication may additionally decrease antipsychotic drug adherence with consequences for both the patient (e.g., illness course and outcome) and the society (e.g., readmissions and longer hospital stays).

Negative opinions and perceptions about medication can be measured using a self-reporting form called Beliefs about Medicines Questionnaire (BMQ) (29), which has been shown useful for patients with severe psychiatric conditions including schizophrenia (28). The primary purpose of this study was to investigate whether cannabis use is associated with negative attitudes toward antipsychotic drugs, as well as medicines in general, in FTP with schizophrenia spectrum disorders. Based on previous literature of cannabis use and negative believes about medication being related to poorer drug compliance, we hypothesized that cannabis use would be linked to negative perceptions of antipsychotic drug treatment.

METHODS

Study Design and Patients

The present cross-sectional study, which was part of the larger Thematically Organized Psychosis (TOP) study, Oslo, Norway, included 265 patients with schizophrenia spectrum disorder who had started their first treatment within the last 12 months. Details regarding recruitment to the TOP-study are described elsewhere (30). In short, the inclusion criteria were (1) age 18–65 years, (2) meeting criteria for a broad schizophrenia spectrum psychosis diagnosis according to the Diagnostic and Structural Manual of Mental Disorders, fourth version [DSM-IV, (31)] (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified), (3) no head trauma, neurological or other medical disorder that could influence CNS functioning, and (4) IQ over 70.

The distribution of diagnoses in the present study was as follows: $N = 160$ (60%) with a diagnosis of schizophrenia, $N = 72$ (27%) schizophreniform disorder, and $N = 33$ (13%) schizoaffective disorder.

All participants gave their informed consent, and the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study.

Clinical Assessments

Sociodemographic history (age, gender, ethnicity, and education), smoking and alcohol use history, and psychiatric history, including duration of untreated psychosis (DUP), hospitalizations, and antipsychotic medications prescribed were obtained through structured interviews. Information on adherence to medication was gathered by the patients themselves, reporting on a scale from 0 to 100%, on how much of their medication they had taken during the past week. All patients were diagnosed with the Structural Clinical Interview for DSM-IV (SCID). Psychotic symptoms were assessed using The Positive and Negative Syndrome Scale (PANSS) (32). Item g12 from PANSS was used as a measure of insight into illness. Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (33). The Global Assessment of Functioning scale (GAF), split version, was used to assess the general level of symptoms and functioning (34) while the Alcohol Use Disorders Identification Test (AUDIT) measured the extent of alcohol use (35).

Measurement of Cannabis Use

Cannabis use was documented through self-reports and information from medical charts, as well as by screening cannabis metabolites in urine. In the present study, we thus had access to data concerning current cannabis use, lifetime cannabis use, and cannabis use disorders according to DSM IV criteria (**Table 1**). Current cannabis use was registered as positive ("yes") if the patient had used cannabis within the last 2 weeks before the assessment. Lifetime use of cannabis was categorized into three groups: never used, used <10 times, or used 10 or more times. We chose to focus on lifetime use of cannabis since it provides a more robust indicator of the extent of cannabis use compared to potential variations in current use, and because consumption also below the threshold for a substance use diagnosis may influence clinical symptomatology in psychosis (36).

TABLE 1 | Cannabis use in the FTP patients.

		N (%)
Current cannabis use	No	190 (72)
	Yes	68 (26)
	Missing data	7 (3)
Lifetime cannabis use	Never	81 (31)
	<10 times	46 (17)
	≥10 times	109 (41)
	Missing data	29 (11)
DSM-IV diagnosis of cannabis use	No	147 (56)
	Abuse	14 (5)
	Dependence	30 (11)
	Missing data	74 (28)

FTP, first treatment for psychosis; N, Number of patients; %, Percentage of patients; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th Edition.

TABLE 2 | Attitudes toward medication as measured by the Beliefs about Medicines Questionnaire (BMQ).

BMQ subscales	*N*	Mean (SD)	Range
"Specific Concerns" subscores	231	17.6 (4.7)	6–30
"Specific Necessity" subscores	230	15.8 (4.4)	5–25
"General Overuse" subscores	233	12.3 (2.7)	4–20
"General Harm" subscores	236	10.6 (2.4)	4–20

BMQ, Beliefs about Medicines Questionnaire; N, Number of patients; SD, Standard deviation.

Measurement of Attitudes Toward Medication

To measure patients' beliefs about their medication, we used the validated Norwegian version of the self-report form Beliefs about Medicines Questionnaire (BMQ) (**Table 2**) (28).

The questionnaire comprises a specific and a general scale, each with two subscales. The first part, BMQ "Specific," assess attitudes toward medicines prescribed for a specific illness focusing on the necessity of taking the medicines and concerns about taking them, divided into "Specific Necessity" and "Specific Concern." "Specific Necessity" has five sections on a 1–5 scale Likert scale (1 = strongly disagree to 5 = strongly agree) covering the extent to which it is considered necessary to take the prescribed medicine (total score range 5–25), while "Specific Concern" consists of six sections covering the degree of concern regarding the use of currently prescribed medicines (total score range 6–30). High scores for "Specific Concerns" represent beliefs that the medications in question (here antipsychotics) have potentially negative consequences, while high scores for "Specific Necessity" indicate the patient's positive perception of the need to take their medications consistently.

BMQ "General" is the second part of the questionnaire, which covers more general beliefs about medicines as treatments, including the risk of overuse and potential for being harmful. The "General Harm" subscale consists of four sections covering notions that medication might be generally harmful, addictive or poisonous and thus should not be taken continuously (total score range 4–20). The "General Overuse" subscale consists of four sections including claims that doctors prescribe too many medications, and that medicines are used too much in general (total score range 4–20 points). High scores for "General Injury" and "General Overuse" indicate overall negative attitudes toward the use of medications as a treatment option.

Statistical Analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Normality of the data was checked using histograms and QQ-plots. Group differences were analyzed using Chi-square tests for categorical variables and analyses of variance (ANOVA), with Tukey *post-hoc* test, for continuous variables. Significant *p*-value was preset to <0.05, two-sided.

For the primary analyses, we used a set of general linear model (GLM) analyses to investigate the relationship between lifetime cannabis use (independent variable) and the different BMQ subscales (dependent variables), controlling for differences in age and gender. Additionally, separate *post-hoc* GLM analyses, controlling for age and gender, were carried out to investigate whether significant group differences as found in the Chi-square and ANOVA tests for demographic factors, lifestyle, or illness-related factors confounded the relationships between lifetime use of cannabis and attitudes to medicine. Preliminary analyses were conducted to ensure assumptions of normality and linearity for the GLMs; no violations of the assumptions were found.

Finally, we conducted *post-hoc* power analyses using the statistical package G*Power (3.1.9.3 for Mac).

Missing Data

There was a lack of data for ∼20% of the patients when combining lifetime cannabis use with BMQ scores. Initial analyses showed that there was no significant difference in sociodemographic factors (age, gender, ethnicity, and total years of education), lifestyle factors (daily tobacco smoking, alcohol use), illness-related factors (age of onset, DUP, total PANSS score, positive PANSS subscores, negative PANSS subscores, depressive symptoms, and global functioning), and use of antipsychotic medications between those who lacked data and those with full datasets ($p > 0.05$ for all).

RESULTS

Sample Characteristics

Table 3 summarizes demographic and clinical characteristics with group comparisons. Patients with lifetime use of cannabis ≥10 times were more likely to be male, of younger age, have a lower age of onset of psychosis and consume alcohol and tobacco more frequently compared to those who have never used cannabis. Patients with lifetime use of cannabis ≥10 times were also more likely to lack insight into illness compared to patients with lifetime cannabis use <10 times, as measured by the PANSS g12 subscore. There were no significant group differences in ethnicity, education, DUP, psychotic symptoms, depressive symptoms, global functioning, current antipsychotic

TABLE 3 | Comparison of lifetime cannabis use vs. demography, lifestyle, illness-related factors, and beliefs about medication in FTP patients.

	Subgroups of lifetime cannabis use	*N*	Mean (SD)/%	*F*/Chi	*P*-value	*Post-hoc* tests for significant group differences in lifetime cannabis use
Demography						
Gender (male)	1. Never	43	28	16.3	<0.001	1 vs. 3. 2 vs. 3
	2. <10 times	24	16			
	3. ≥10 times	85	56			
Age (year)	1. Never	81	28.8 (8.7)	6.2	0.002	1 vs. 3
	2. <10 times	46	26.9 (9.2)			
	3. ≥10 times	109	25.0 (5.3)			
Ethnicity (Caucasian)	1. Never	59	32	1.4	0.51	NA
	2. <10 times	37	20			
	3. ≥10 times	88	48			
Education (total years)	1. Never	80	13.0 (3.0)	2.6	0.08	NA
	2. <10 times	46	12.3 (3.0)			
	3. ≥10 times	109	12.2 (2.0)			
Tobacco smoking (daily)	1. Never	25	18	48.7	<0.001	1 vs. 2. 1 vs. 3
	2. <10 times	32	22			
	3. ≥10 times	86	60			
Alcohol use (AUDIT total score)	1. Never	72	4.8 (5.5)	7.7	<0.001	1 vs. 3
	2. <10 times	41	7.1 (7.6)			
	3. ≥10 times	95	9.2 (8.1)			
Illness-related factors						
Age of onset of psychosis	1. Never	79	24.9 (8.6)	4.1	0.02	1 vs. 3
	2. <10 times	45	22.2 (8.2)			
	3. ≥10 times	108	21.9 (5.7)			
DUP (weeks)	1. Never	79	155.1 (269.9)	1.2	0.29	NA
	2. <10 times	46	169.7 (217.4)			
	3. ≥10 times	108	117.1 (164.9)			
Overall psychotic symptoms (PANSS total score)	1. Never	81	67.7 (16.5)	0.6	0.53	NA
	2. <10 times	46	64.9 (16.4)			
	3. ≥10 times	109	68.0 (15.9)			
Positive symptoms (PANSS positive subscores)	1. Never	81	16.6 (5.2)	1.25	0.29	NA
	2. <10 times	46	15.7 (5.7)			
	3. ≥10 times	109	17.2 (5.4)			
Negative symptoms (PANSS negative subscores)	1. Never	81	16.4 (6.7)	0.38	0.68	NA
	2. <10 times	46	15.7 (6.0)			
	3. ≥10 times	109	16.7 (6.2)			
Lack of insight (PANSS g12 subscore)	1. Never	81	2.7 (1.5)	6.14	0.003	2 vs. 3
	2. <10 times	46	2.2 (1.3)			
	3. ≥10 times	109	3.1 (1.4)			
Depressive symptoms (CDSS total score)	1. Never	73	6.6 (5.2)	1.36	0.26	NA
	2. <10 times	44	7.2 (5.2)			
	3. ≥10 times	106	5.8 (4.8)			
Global functioning (GAF-F subscore)	1. Never	81	42.1 (10.8)	0.75	0.47	NA
	2. <10 times	46	40.2 (9.6)			
	3. ≥10 times	109	40.3 (9.7)			
Global symptoms (GAF-S subscore)	1. Never	81	39.6 (7.8)	0.93	0.40	NA
	2. <10 times	46	40.8 (11.1)			
	3. ≥10 times	109	38.6 (9.8)			
Current antipsychotic use	1. Never	62	32	3.66	0.16	NA
	2. <10 times	38	20			
	3. ≥10 times	95	49			

(Continued)

TABLE 3 | Continued

	Subgroups of lifetime cannabis use	*N*	Mean (SD)/%	*F*/Chi	*P*-value	*Post-hoc* tests for significant group differences in lifetime cannabis use
Self-reported adherence to medication (%)	1. Never	59	86 (35)	0.52	0.60	NA
	2. <10 times	38	79 (41)			
	3. ≥10 times	91	81 (39)			
Beliefs about medication (BMQ)						
BMQ "Specific" total scores	1. Never	64	33.2 (5.5)	1.24	0.29	NA
	2. <10 times	39	34.6 (5.6)			
	3. ≥10 times	98	32.9 (6.1)			
BMQ "Specific Necessity" subscore	1. Never	65	15.3 (4.3)	1.28	0.28	NA
	2. <10 times	39	16.7 (4.8)			
	3. ≥10 times	99	15.6 (4.3)			
BMQ "Specific Concern" subscore	1. Never	65	17.9 (4.6)	0.42	0.66	NA
	2. <10 times	40	18.1 (4.5)			
	3. ≥10 times	98	17.4 (4.8)			
BMQ "General" total scores	1. Never	66	22.9 (4.9)	0.03	0.97	NA
	2. <10 times	40	23.2 (4.1)			
	3. ≥10 times	98	23.1 (4.3)			
BMQ "General Harm" subscore	1. Never	66	10.6 (2.6)	0.29	0.75	NA
	2. <10 times	41	10.9 (2.2)			
	3. ≥10 times	101	10.7 (2.4)			
BMQ "General Overuse" subscore	1. Never	68	12.4 (2.9)	0.10	0.91	NA
	2. <10 times	40	12.2 (2.6)			
	3. ≥10 times	98	12.4 (2.7)			

FTP, first treatment for psychosis; N, number of patients; SD, standard deviation; %, percentage; F, F-test; Chi, Chi-square test; NA, not applicable; AUDIT, alcohol use disorder Identification Test; DUP, duration of untreated psychosis; PANSS, positive and negative syndrome scale; CDSS, calgary depression scale for Schizophrenia; GAF-F/S, the global assessment of Functioning scale (GAF, split version); BMQ, beliefs about medicines questionnaire information on adherence to medication was gathered by the patients themselves, reporting on a scale from 0 to 100%, on how much of their medication they had taken during the past week. P-values are obtained from one-way ANOVA and Chi-square test. For p-values that were significant in the ANOVA and Chi-square tests, group differences in lifetime cannabis use were examined by post-hoc Tukey.

treatment, or self-reported adherence to medication between the three cannabis use groups.

The Relationship Between Lifetime Cannabis Use and Beliefs About Medication

After controlling for age and gender, patterns of lifetime cannabis use were not associated with negative perceptions about medication, neither specific beliefs about antipsychotic medication nor general beliefs about pharmacotherapy in general as measured by the BMQ (**Table 4**).

Similarly, current use of cannabis or a DSM-IV diagnosis of cannabis use disorders was not associated with BMQ subscores ($p > 0.05$). Moreover, *post-hoc* GLM analyses based on lifetime use of cannabis controlling for age and gender, as well as separately controlling for the measures that were significant in the group comparisons tests (i.e., daily smoking, alcohol use, age of onset of psychosis, and lack of insight into illness), did not show any significant associations between lifetime use of cannabis and BMQ subscores (all $p > 0.05$).

Post-hoc power analyses showed that the statistical power in our study was 0.5 for the lifetime cannabis use against BMQ subscores; thus, medium power. The power analyses also showed that for achieving a strong power (>0.8) we would have needed a sample size of 408 subjects.

DISCUSSION

The main finding of the present study was that a history of cannabis use was not associated with negative beliefs about medications as measured with the BMQ in FTP. To our knowledge, this is the first study that has examined this relationship.

Previous studies of psychotic patients have indicated that negative beliefs about medications are major reasons for non-adherence to antipsychotic drug treatments (37, 38); and likewise, that cannabis use is a risk factor for poor adherence to drug treatment (23). While we initially hypothesized to find a link between cannabis use and negative believes about medication, the results of the present study do not support such a link. This could suggest that the relationship between cannabis use and poor adherence to medication may not necessarily be influenced or mediated by negative beliefs about drug treatment. Still, other reasons for a lack of association should also be considered. One important factor is type II error related to sample size. In the *post-hoc* power analyses, we found that the power was 0.5 indicating

TABLE 4 | General linear model (GLM) analyses examining the relationship between lifetime cannabis use and beliefs about medication (BMQ) in patients with FTP.

	F	df	*P*-values	Adjusted *R* squared for the whole model
BMQ "Specific" total scores				
Age	2.71	1	0.10	0.009
Gender	0.60	1	0.44	
Lifetime cannabis use	0.99	2	0.37	
Error		196		
BMQ "Specific necessity" subscore				
Age	1.90	1	0.17	−0.006
Gender	0.00	1	0.97	
Lifetime cannabis use	0.23	2	0.80	
Error		198		
BMQ "Specific Concern" subscore				
Age	0.39	1	0.53	−0.002
Gender	0.71	1	0.40	
Lifetime cannabis use	1.23	2	0.30	
Error		198		
BMQ "General" total scores				
Age	0.25	1	0.62	−0.015
Gender	0.66	1	0.42	
Lifetime cannabis use	0.09	2	0.91	
Error		199		
BMQ "General Harm" subscore				
Age	5.80	1	0.02	0.012
Gender	0.18	1	0.68	
Lifetime cannabis use	0.46	2	0.63	
Error		203		
BMQ "General Overuse" subscore				
Age	1.66	1	0.20	−0.005
Gender	1.15	1	0.28	
Lifetime cannabis use	0.14	2	0.87	
Error		201		

FTP, first treatment for psychosis; BMQ, beliefs about medicines questionnaire; F, F-test; df, degrees of freedom. Analyzed with GLM models while controlling for age and gender.

a medium sized power, and that a sample size of 408 would have been needed for achieving a strong power (>0.8). It is therefore possible that our sample size was insufficient for detecting weaker associations between lifetime cannabis use and negative beliefs about medication. Additionally, our data showed that in FTP with limited exposure to antipsychotic drug treatment the mean BMQ scores were in the middle of the scales (i.e., neither predominantly negative nor positive about medication) and the standard deviation between 2.4 and 4.7. The relatively neutral beliefs about drug treatment in this group of patients could have precluded us from observing a link. Moreover, it is reasonable to anticipate that current symptomatology may impact the acceptance of treatment. For instance, patients who have persecutory delusions may be disinclined to take prescribed medication. Cannabis use has also been associated with more severe positive/psychotic symptoms (10, 39). However, in the current study we found no significant differences in psychotic symptoms between the three lifetime cannabis groups. This may suggest that the participants were recruited in a stable phase of illness with low symptom levels that could influence any negative beliefs about medication.

We found that close to 70% of the participants had used cannabis at some point in their lives, with nearly 50% reporting frequent use (≥10 times) and 25 % meeting the DSM-IV diagnosis of cannabis use disorders, in accordance with previous findings (40, 41). Additionally, we found a significant gender effect with a higher prevalence of frequent cannabis use in males, in line with a recent Norwegian study of patients with FTP (42) and several prior studies (6, 43). Moreover, cannabis users were younger than those with no prior use (11, 16, 17), had higher alcohol consumption (44–46), were more often smokers (47), had a lower age at onset of psychosis (39, 48, 49), and showed poorer insight into illness (23); indicating that our sample, despite of the possible limitations described in the previous section, may be representative of FTP and that our findings could generalize outside of the current settings.

Limitations

The sample consisted of psychiatric patients who had given informed consent to participate in a comprehensive research project, this might have caused a bias in the direction of more adherent patients in our sample. It is also possible that patients who are skeptical about doctors, medical treatment or research, as well as those with more pronounced delusions, may have said no to be included in the study. Our patients were relatively young and with limited antipsychotic experiences, this could have resulted in more neutral BMQ scores. Our results may therefore not necessarily be transferable to chronic patients. Also, we did not have information on whether the patients met the criteria for DSM-IV diagnosis of tobacco and/or alcohol abuse and dependence. Additionally, the study was medium powered and well-powered studies are needed before firm conclusions can be made.

Strengths and Clinical Implications

To our knowledge, this is the first study in a psychosis cohort that has specifically examined a relationship between cannabis use and negative perceptions toward medication. The FTP sample was well-characterized, allowing us to examine group differences in demographic, lifestyle, illness, and treatment related factors.

Cannabis use and poor compliance to antipsychotic medication is a huge problem in patients with psychosis. Not only does it affect the lives of the patient in terms of poorer illness course and outcome, but it also effects their care givers and the society, e.g., readmissions to hospitals and extended stays in hospital wards. In order to device targeted approaches to address this problem of poor compliance, it is important to understand any additional factors that may contribute to poor drug adherence. The findings of the present study may therefore be of clinical relevance as they could point to other factors besides negative attitudes and believes about medication being important for poor adherence in cannabis

users and that other aspects of cannabis use should be explored in future studies in order to improve treatment adherence in this patient group.

CONCLUSION

The present study show that a history of cannabis use is not associated with negative perceptions toward medications among patients with FTP. This may be a characteristic of an FTP sample with limited positive and negative experiences with antipsychotic treatments, and illness development could change their attitudes. Future studies should examine this association in well-powered longitudinal studies with multiple time points and objective adherence measures to better understand the relationship between cannabis use, believes about medication, and adherence to drug treatment.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because sharing of data to external parties has not been approved by the Ethics Committee. Requests to access the datasets should be directed to PG, prig@norceresearch.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical Research Ethics. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS designed the study, together with IM and VS. PG and SS analyzed the data and were responsible for interpretation of results together with IM and VS. PG drafted the first version of the manuscript together with IM and VS. OA, NS, TV, and ER contributed with data. All authors contributed to the writing of the manuscript and approved the final version.

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Anti-Neuronal Autoantibodies (Cell Surface and Onconeural) and Their Association With Natural Autoantibodies in Synthetic Cannabinoid-Induced Psychosis

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Patients suffering from encephalitis may present psychiatric symptoms; however, the clinical relevance of anti-neuronal antibodies in patients experiencing a psychotic episode without encephalitis is still unclear. In this study, we examined the presence of anti-neuronal cell surface autoantibodies and onconeural autoantibodies in serum samples of 22 synthetic cannabinoid users presenting with psychosis. We found only two positive cases; however, seven patients had borderline results. Nonetheless, we found no significant correlation between anti-neuronal autoantibodies and the intensity of psychosis indicated by the Positive and Negative Syndrome Scale (PANSS) scores. The length of drug use and the combination of other drugs with synthetic cannabinoids have no significant effect on anti-neuronal autoantibody positivity. Nonetheless, the ratio of anti-citrate synthase (anti-CS) IgM and IgG natural autoantibodies was significantly lower ($p = 0.036$) in the anti-neuronal autoantibody-positive/borderline samples, than in the negative group. Interestingly, anti-CS IgM/IgG showed a significant negative correlation with PANSS-positive score ($p = 0.04$, $r = -0.464$). Our results demonstrated that anti-neuronal autoantibody positivity occurs in synthetic cannabinoid users, and the alteration of anti-CS IgM/IgG natural autoantibody levels points to immunological dysfunctions in these cases.

Keywords: autoimmune encephalitis, synthetic cannabinoid, anti-citrate synthase antibodies, psychosis, anti-neuronal autoantibodies, natural autoantibodies

INTRODUCTION

The etiology of psychosis is complex and multifactorial; immunological hypothesis has recently become increasingly prominent in psychiatric research. Multiple studies have identified associations between infections or autoimmune diseases and psychotic disorders (1). The autoimmune neurological disease, N-methyl-D-aspartate (NMDA)-encephalitis, frequently occurs with symptoms characteristic of mental disease (2, 3). A systematic review showed that among patients who are treated with first episode psychosis, anti-neuronal antibodies, including anti-NMDA, were present at a higher rate than in controls (4). Other cell surface autoantibodies, such

as voltage-gated potassium channel (VGKC) antibodies, are associated with limbic encephalitis along with insomnia, autonomic dysfunction, neuromyotonia, and cognitive dysfunction in a disease called Morvan syndrome (5). A case report suggests that an onconeural autoantibody, called anti-Yo antibody, might play a role in the induction of psychosis without paraneoplastic neurological syndrome (6). Several other anti-neuronal antibodies have been reported in patients with psychosis or in patients with encephalitis showing psychotic symptoms (7, 8). Therefore, autoantibodies directed against neuronal cell surface or intracellular antigens may have a probable role in mental diseases, especially in psychosis. Nonetheless, the clinical relevance of any of these autoantibodies in patients with psychosis without encephalitis is still not known. Natural antibodies are present in healthy individuals without prior antigenic stimulation, and also in patients with autoimmune diseases (9). Naturally occurring autoantibodies of the IgM isotype are thought to provide protection against autoimmune reactions associated with pathological autoantibodies. The level of natural IgG autoantibodies in sera is higher in patients with various diseases than in healthy individuals and they may represent a breakdown in central tolerance (10).

Synthetic cannabinoid receptor agonists (SCRAs) were synthetized in the 1960s to investigate possible therapeutic effects, and to study cannabinoid receptors (11). In the early 2000s, variations in SCRAs started to sell commercially, by the name "K2, Herbal, Spice, Mojo" and by many other names. They are popular among younger adults and teenagers, because they are cheap, "natural," and undetectable during routine drug screening. SCRAs mostly have the same effect as tetrahydrocannabinol (THC), which can be found in marihuana. Several studies suggest the potential effect of SCRAs in the treatment of some psychiatric disorders. Medical cannabis and synthetic cannabinoids, both acting on the endocannabinoids system, may have a potential therapeutic use for improving posttraumatic stress disorder (PTSD) and schizophrenia symptoms or inhibit pain (12, 13). Most studies emphasize the immunosuppressive effect of THC and cannabidiol (CBD) (14, 15). Moreover, THC and CBD are currently being investigated as potential therapeutic agents for several inflammatory or autoimmune diseases. However, a few studies suggest their proinflammatory effect in the brain (15). Similar to THC SCRAs bind to cannabinoid receptor 1 (CB1) and to cannabinoid receptor 2 (CB2) and stimulate CB1 more than CB2. CB1 are found in the central nervous system, especially in the cerebral cortex, hippocampus, cerebellum, and basal ganglia. CB2 are mostly expressed by immune (macrophage and B cells) and hematopoietic cells; thus, stimulation of CB2 has immunomodulatory effects (11, 16). CB2 seems to play an important role in the immune mechanism in the central nervous system (17). Several case reports suggest that cannabis can cause vasculitis both in peripheral arteries and in the central nervous system by autoimmune reactions (18–20). THC exposure during adolescence also resulted in a persistent neuroinflammatory state in adult female rats and mice, characterized by altered microglia morphologic structure, increased proinflammatory mediators, reduced CB1, and increased CB2 (21). A few case reports show that SCRA users can develop autoimmune disease (22, 23). The study by Parajuli et al. represents a case about a drug-induced posterior reversible encephalopathy syndrome (PRES) after K2 consumption (a type of SCRAs); besides, the autoimmune mechanism of a toxic origin can be found in the background of PRES (24). Furthermore, in our previous study, we reported the case of a teenager who used SCRA and was diagnosed with NMDA encephalitis (16). However, the relationship between the use of SCRAs and the presence of anti-neuronal antibodies was not investigated in detail. Consequently, the main purpose of this study was to find correlations between anti-neuronal antibodies and the intensity of psychosis indicated with Positive and Negative Syndrome Scale (PANSS) score in SCRA users. Further aim was to search for possible associations between natural autoantibodies and anti-neuronal autoantibodies with possible relevance to the assessment of the severity of drug-induced psychosis.

METHODS

Patients

The study is based on the data of 22 patients with suspected SCRAs-induced psychosis (**Table 1**). All the patients underwent a comprehensive psychiatric evaluation and assessment of acute psychotic exacerbation of PANSS. Inclusion criteria were as follows: psychosis after using SCRAs, adolescents and young adults (age between 13 and 32 years), normal serum electrolytes, blood counts, kidney, and liver function, and signed written informed consent form. General exclusion criteria were the diagnosis of schizophrenia, schizoaffective psychosis, bipolar disorder, autoimmune disorders, and ongoing infection. The study was approved by the Regional Clinical Research Committee (5951-PTE2015). Peripheral blood was collected and allowed to clot for at least 30 min before centrifugation for 10 min at 1,000 × *g*. Serum was removed and stored at −80°C until performing the tests for determination of autoantibodies.

TABLE 1 | Characteristics of patients.

Characteristics	Synthetic cannabinoid users (*n* = 22)
Age (years), mean (SD)	17 (4.9)
Sex (male), *n* (%)	19 (86.4%)
Family history (positive for addiction), *n* (%)	5 (22.7%)
Polytoxicomania (yes), *n* (%)	9 (40.9%)
Drug use (month), mean (SD)	23.8 (23.5)
PANSS total, mean (SD)	55 (18)
PANSS general, mean (SD)	32.6 (8.7)
PANSS positive, mean (SD)	11.7 (7.6)
PANSS negative, mean (SD)	11.1 (5.5)

PANSS, Positive and Negative Syndrome Scale.

TABLE 2 | Clinical features and autoantibody results of each case.

Age and sex	Previous history of psychiatric disorders	Duration of drug use (in months)	Substances	Cell surface antigens	Onconeural antigens	PANSS positive	PANSS negative	PANSS general	PANSS total
15, male	–	48	SCRA	negative	Yo borderline	9	10	22	41
16, male	1	6	SCRA	negative	Rec borderline	7	7	25	39
17, male	–	9	SCRA	negative	negative	7	27	46	80
16, male	–	3	SCRA	negative	Hu borderline	7	7	32	46
15, male	–	–	SCRA, other NPS	negative	Tr borderline	26	13	54	93
17, male	–	–	SCRA	negative	SOX1 borderline	7	7	31	45
15, male	–	3	SCRA	negative	negative	10	7	34	51
13, female	2	<1	SCRA	negative	negative	7	11	32	50
17, female	3	60	SCRA	negative	negative	7	7	26	40
16, male	3	48	SCRA, NC, LSD, other NPS, MDMA, amphetamine	negative	Amp positive	7	14	35	56
17, male	3	3	SCRA, NC	negative	negative	7	7	34	48
15, female	4	4	SCRA	negative	negative	7	7	22	36
17, male	–	<1	SCRA	negative	negative	7	10	32	49
15, male	3	24	SCRA	negative	negative	7	7	28	42
13, male	1	18	SCRA	negative	negative	7	7	32	46
14, male	5	60	SCRA, cocaine, other NPS	negative	Rec borderline	7	13	27	47
17, male	–	60	SCRA, amphetamine, NC	negative	negative	23	8	32	63
15, male	4	36	SCRA, NC, MDMA, cocaine	negative	negative	7	13	30	50
17, male	–	60	SCRA	negative	negative	23	16	46	85
19, male	–	8	SCRA, BDZ	negative	negative	24	19	41	84
32, male	6	17	SCRA, other NPS	negative	negative	28	21	39	88
30, male	7	6	SCRA, cocaine, heroin, NC	CASPR2 positive	negative	16	7	17	40

Previous history of psychiatric disorders:

1. Attention deficit hyperactivity disorder
2. Emotional disorders with onset specific to childhood
3. Unspecified behavioral and emotional disorders with onset usually occurring in childhood and adolescence
4. Adjustment disorders
5. Mild mental retardation
6. Personality disorder, unspecified
7. Other acute and transient psychotic disorders

SCRA, Synthetic Cannabinoid Receptor Agonist; NPS, New Psychoactive Substances; NC, Natural Cannabis; MDMA, 3,4-methylenedioxymethamphetamine; LSD, Lysergic Acid Diethylamide; BDZ, Benzodiazepine.

Detection of Anti-Neuronal Autoantibodies

The anti-neuronal autoantibodies were detected either with indirect immunofluorescence or immunoblot techniques. IgG antibodies directed against neuronal cell surface antigens, including N-methyl-D-aspartate-type glutamate receptor (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA1, AMPA2), contactin-associated protein 2 (CASPR2), leucine-rich glioma-inactivated protein 1 (LGI1), and gamma- aminobutyric acid beta receptor (GABA B receptor), were detected simultaneously using a biochip mosaic of transfected HEK293 cells expressing these six antigens of interest (Autoimmune Encephalitis Mosaic 1; Euroimmun, Lübeck, Germany). Samples were classified as positive, borderline, or negative based on the fluorescence intensity of the transfected cells. Onconeural antibodies (IgG antibodies targeting intracellular antigens), namely, glutamic acid decarboxylase-65 (GAD65), collapsin response mediator protein 5/crossveinless-2 (CV2), type 1 anti-neuronal nuclear antibody (ANNA-1, Hu), Ri, Yo, Ma2/Ta, zinc finger protein 4 (ZIC4), amphiphysin (Amp), recovering (Rec), titin, sry-like high mobility groupbox protein1 (SOX1), and Tr/delta notch-like epidermal growth factor-related receptor (DNER),

were determined using EUROLINE paraneoplastic neurologic syndromes 12 Ag test (Euroimmun, Lübeck, Germany). For the evaluation of the test strips, the recommended EUROLineScan software was used, which automatically identifies the bands on the test strip and measures their intensity. Based on the intensity of the bands, the result of the autoantibody test can be negative, borderline, or positive.

Measurement of Natural Autoantibodies

We have previously shown that antibodies directed against citrate synthase belong to the pool of natural autoantibodies (9). The levels of anti-citrate synthase (anti-CS) IgM and IgG autoantibodies were determined with an in-house ELISA, as previously described (9). Briefly, 96-well polystyrene plates were coated with 100 µl of 5 µg/ml citrate synthase from porcine heart (Sigma, St Louis, MO, USA) at 4–8°C overnight. Following the saturation of nonspecific binding sites, serum samples were incubated in duplicate at 1:100 dilution for 1 h at room temperature. Finally, the plate was incubated with horseradish peroxidase (HRP)-conjugated anti-human IgM or IgG-specific antibodies (Dako, Glostrup, Denmark) for 1 h at room temperature; the reaction was developed with TMB and measured at 450 nm, using an iEMS MF microphotometer (Thermo Labsystem, Beverly MA, USA).

Statistical Analysis

Statistical evaluation was performed with SPSS v. 27.0 statistics package (IBM, Armonk, NY, USA). Continuous variables were compared with the Mann-Whitney *U* test; Fischer's exact test was used to find the difference between categorical variables. Relationship between continuous variables was assessed with Spearman correlation. A $p < 0.05$ was considered significant.

RESULTS

Samples of eight of the 22 patients (36.4%) had positive or borderline results for anti-neuronal autoantibodies. One patient (4.5%) was positive for the antibody against CASPR2 from the neuronal cell surface antigens. One patient (4.5%) showed anti-AMP positivity, and six patients (27.3%) had a borderline result for other onconeural antibodies targeting Rec, Yo, Hu, SOX1, and Tr. None of these patients received a diagnosis of autoimmune encephalitis (**Table 2**).

The clinical background of two interesting adolescent patients is presented, one with long-term drug use (for 4 years) and another with short-term drug use (for 6 months) (**Table 3**). Both patients are anti-neuronal antibody-positive or borderline cases.

For statistical analyses, patients with positive and borderline results for anti-neuronal autoantibodies were considered as one group. We found no significant difference in PANSS-total, PANSS-positive, PANSS-negative, and PANSS-general scores between patients with positive/borderline and negative results. The length of drug use and the combination of other drugs with synthetic cannabinoids had no significant effect on anti-neuronal autoantibody positivity.

TABLE 3 | Case vignettes for two patients with positive or borderline anti-neuronal antibody test result.

Case vignette 1
Case 1 was a 16-year-old adolescent who had been using drugs for 4 years; previously, he had consumed different drugs. In the past period, he used synthetic cannabinoids; the last time when he used it was on the same day of admittance to hospital. His serum sample was positive for anti-AMP antibody. After his admission, he tried to escape many a times, and he was aggressive with the nurses. He had psychomotor agitation, acoustic hallucination, and had suicidal intention after using synthetic cannabinoids. He tried to stop using drugs but failed.
Case vignette 2
Case 2 was a 16-year-old adolescent who had been using drugs for 6 months. He was adopted and started using synthetic cannabinoids when his foster mother died. He admitted not using drugs for 2 weeks. Anti-Rec antibody was borderline in his laboratory findings. He behaved aggressively due to substance use in the past months. He had burst of anger many a times against his mates, and he damaged the furniture in the orphanage. Once he threatened his classmate with an alarm gun.

We also looked for alterations in the level of natural anti-CS IgM and IgG autoantibodies between patients with anti-neuronal autoantibody-positive/borderline and negative results. We found no significant differences neither in the level of anti-CS IgM (**Figure 1A**) nor in the level of anti-CS IgG antibodies (**Figure 1B**) between the anti-neuronal autoantibody-positive/borderline and the negative group; however, the level of anti-CS IgG showed a higher trend in patients with anti-neuronal autoantibody-positive/borderline results than in patients with negative results (**Figure 1B**). Therefore, we also analyzed the ratio of anti-CS IgM and IgG between these patient groups and found that it was significantly lower ($p = 0.036$) in the anti-neuronal autoantibody-positive/borderline group than in the negative group (**Figure 1C**). Next, we evaluated the possible associations between the number of anti-CS IgM, IgG antibodies, their ratio, and the severity of symptoms measured by PANSS-total, PANSS-positive, PANSS-negative, and PANSS-general scores. Interestingly, the ratio of anti-CS IgM and IgG showed a significant negative correlation with PANSS-positive score ($p = 0.04$, $r = -0.464$).

DISCUSSION

The usage of recent designer drugs, including substituted cathinones (mephedrone, methylone, often called as "bath salts"), SCRAs and synthetic hallucinogens (N-bomb) expanded in the past decade, and they are well-known in the market, especially among the young population. Compound availability has changed rapidly, and it is hard to detect these substances on the routine urine drug test (25). The purchase via internet is cheap, as "legal high" promotes widespread use among adolescents. SCRA users are usually poorly educated and mostly males (25–27); in agreement with this, 86.4% of the patients in our study were males. Besides the stimulatory effect of these drugs, acute toxicity and psychosis may occur. Some toxicology reports highlighted the main presenting features

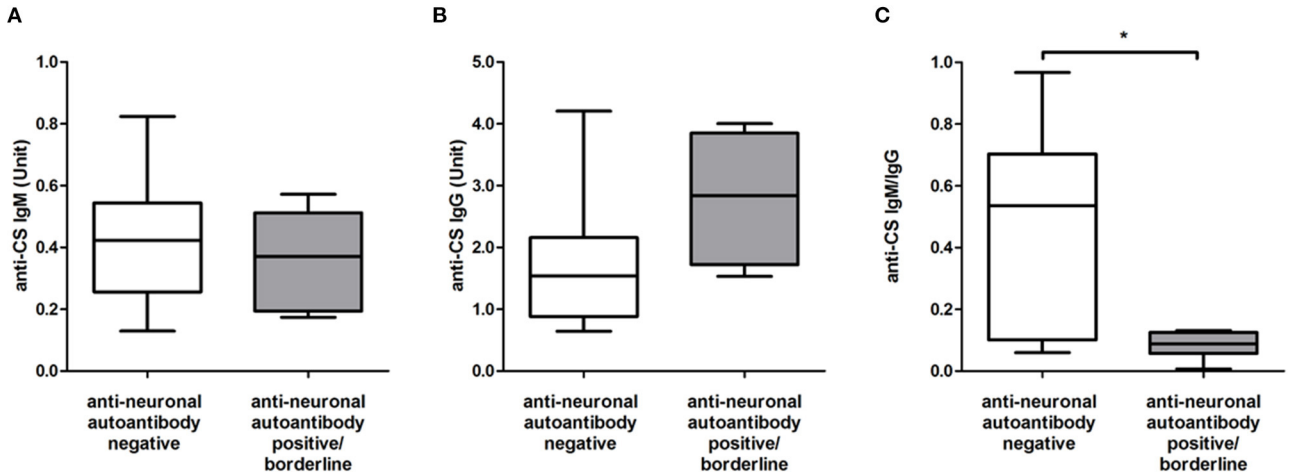

FIGURE 1 | The level of anti-citrate synthase (CS) IgM **(A)**, IgG **(B)**, and autoantibodies and their ratio **(C)** in patients with positive/borderline ($n = 8$) and negative ($n = 14$) results for anti-neuronal autoantibodies. The boxes show interquartile ranges (IQR); the horizontal lines represent medians and the whiskers indicate the lowest and highest values. $^*p < 0.05$.

being toxic psychosis and delirium (40%), agitation (10%), and hallucinations (4–7%) (25, 26, 28). SCRA users had higher levels of positive PANSS than THC users. Greater toxicity can be attributed to pharmacological features: SCRAs show 50–300 times greater affinity for the CB1 than THC and they are full agonists at CB1 (27). A report suggests that CB1 antagonist rimonabant could be a treatment option for the management of SCRA overdose (29). Rimonabant was used as an antiobesity drug, but it was withdrawn in Europe because of psychiatric side effects in 2008. Additional studies are required to apply for its possible application in other medical conditions. Cannabinoids can modulate immune reactions in the brain (17), and in our study, we found that 36.4% of the patients with SCRA-induced psychosis had a positive or borderline result for anti-neuronal autoantibodies. Among the autoantibodies against neuronal cell surface antigens, the one most commonly investigated is the anti-NMDA antibody. A recent study found anti-NMDA IgG in 8.6% patients suffering from schizophrenia, but interestingly, healthy controls showed an even higher rate (10.8%) of positivity (30, 31). However, none of the patients in our study had anti-NMDA antibody. LGI1 and CASPR2 antibodies are currently classified as VGKC complex antibodies and are commonly considered to have the same clinical significance (32). There are cases where anti-VGKC complex disease initially presented with schizophreniform psychiatric disease (33, 34). In our study, only one patient had a borderline result for the antibody against CASPR2. Onconeural antibodies were suggested to contribute to immunological alterations in patients with psychiatric disorders, but the literature on these antibodies in psychiatric diseases is scarce (21). Anti-Hu and anti-Yo antibodies were shown to induce neuronal and Purkinje-cell death in the hippocampal and cerebellar regions of rats (35–37). Case reports suggested that anti-Yo and anti-Ri onconeural antibodies may play a role in autoimmune processes in patients with psychiatric disease (6, 38, 39). Only one of our patients was positive for anti-Amp antibody, two patients had borderline result for anti-Rec, and four patients showed a borderline result for anti-Yo, anti-Hu, anti-SOX1, or anti-Tr antibodies. We did not find any significant correlations between anti-neuronal antibodies and the PANSS scores of the investigated patients, suggesting that anti-neuronal antibodies do not influence the severity of SCRA-induced psychosis. Neuroscientific studies have identified atypical dopamine activity in cannabis users, which therefore could underlie its association with psychosis in SCRA users (40). In our previous studies, we detected natural autoantibodies directed against CS in healthy individuals and patients with autoimmune diseases (9, 41, 42). Natural IgM autoantibodies are polyreactive; they recognize evolutionally conserved self-structures and serve as scavengers of damaged molecules and cells. They participate in the removal of apoptotic cells and maintain tissue homeostasis, and therefore, have been implicated in the control of inflammation and immunological balance (43–45). The majority of natural autoantibodies was originally thought to be of IgM isotype, but later, the presence of natural IgG autoantibodies was also described and their presence could be the result of an adaptive-like immune response (9, 42). Under pathological conditions, a compensatory increase in IgG antibodies with anti-idiotypic activity can occur (46), and previously, we found an elevated level of anti-CS IgG antibodies in patients with systemic lupus erythematosus positive for anti-dsDNA IgG (41). Consequently, the higher trend in anti-CS IgG level, which resulted in an decreased ratio of anti-CS IgM/IgG autoantibodies in patients with anti-neuronal autoantibody-positive/borderline results, may be a harbinger of autoimmune phenomena.

We can conclude that the presence of anti-neuronal autoantibodies in serum samples of patients acutely admitted to hospital with a psychotic episode induced by SCRAs abuse is not exceptional; however, routine screening for these antibodies

is not likely to be informative in most cases. According to our results, testing for anti-neuronal antibodies in serum cannot be suggested for diagnostic purposes in patients using SCRA, as their detection has no therapeutic impact on these cases. Additional studies are required to check the presence of these antibodies in the cerebrospinal fluid (CSF). To our knowledge, this is the first study addressing the prevalence of anti-neuronal and natural autoantibodies among SCRA users. Our study has the limitation that healthy or other psychotic adolescent controls were not enrolled, but for a pediatric patient group, it is hard to find age-matched healthy volunteers with the permission of parents. Nevertheless, our aim was to investigate the relevance of anti-neuronal autoantibody positivity in SCRA users. Other limitation of this study was the negative result of urine and serum tests for synthetic cannabinoids. The clinical challenge of these substances is that the chemical variety makes monitoring difficult.

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 Regional Clinical Research Committee (5951-PTE2015). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TT and DS designed the study. LH, GC, TT, SE-B, ZC, and DS performed the experiments. LH, GC, NL, MK, and TT contributed to the clinical data. LH, TB, and DS analyzed the data. LH and DS wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version of the manuscript.

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Using Experience Sampling Methodology Data to Characterize the Substance Use of Youth With or At-Risk of Psychosis

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Objectives: Psychotic-spectrum disorders emerge during adolescence and early adulthood, which corresponds with the peak period for substance use initiation. Clinical and epidemiological data provide support that substance use is associated with psychotic symptom onset and severity. Experience-sampling methodology (ESM) data may provide additional insight into dynamic associations between substance use and psychotic symptoms. This is one of the first efforts to characterize substance use frequency and dynamic associations with psychotic symptoms and negative affect from ESM data in both clinical high risk (CHR) and early psychosis (EP) individuals.

Methods: Using ESM, 33 individuals, including 17 with CHR and 16 EP (age range: 15–24), provided information on substance use, negative affect, and psychotic symptoms 6 times a day across a 21-day data collection window. Psychotic symptoms and negative affect included multi-item variables rated on a seven-point Likert Scale. Participants reported recent substance use for 4 drug classes (nicotine, cannabis, depressants, stimulants) via a yes/no item. Descriptive information included data on substance use frequency, and momentary negative affect and psychotic symptoms. Exploratory analyses included multi-level and person-level dynamic structural equation models, which assessed contemporaneous and lagged associations between substance use and symptoms.

Results: Twenty-seven individuals (82%) reported recurrent substance use including stimulants (n = 12, 46%), nicotine (n = 9, 27%), cannabis (n = 6, 18%), and depressants (n = 4, 12%). Individuals with any recurrent substance use indicated usage at 47.7% of answered prompts; stimulants at 23.6%; nicotine at 74.2%; cannabis at 39.1%; and depressants at 20.1%. A multi-level dynamic structural equation model reflected that substance use (any class) was associated with lagged negative affect ($\beta = -0.02$, CI: −0.06, <-0.00) but no significant contemporaneous or lagged associations between substance use and psychotic symptoms. Person-level models suggest potentially meaningful inter-individual variability.

Conclusions: CHR and EP individuals use a range of substances that may both reflect and influence other experiences in daily life experiences. Data reflected moderate to high rates of recurrent substance use with more consistent use within nicotine and cannabis classes. ESM data have the potential to increase our understanding of the dynamic relationships between substance use and symptoms and to inform treatment for individuals in early course psychosis.

Keywords: psychotic-spectrum disorders, ecological momentary assessment, early psychosis, psychotic symptom, negative affect, dynamic association, momentary data

INTRODUCTION

Individuals with psychotic spectrum disorders are more likely to have substance use disorders compared to the general population (1, 2). Studies report elevated rates of substance use in individuals at-risk of psychosis or with first-episode psychosis across substance categories, including cannabis (42–54%), nicotine (16–75%), alcohol (17–44%), and stimulants (7–45%) (1, 3–6). Developmentally, psychotic-spectrum disorders emerge during adolescence and early adulthood, a period of time that overlaps with the peak ages for substance use initiation (7). Given this timing and the considerable comorbidity of substance use and psychotic disorders, greater understanding of the associations between substance use and psychotic symptoms is needed to help guide treatment, especially during the early stages of psychosis.

Prior studies suggest that (1) substance use contributes to earlier onset of psychosis and worsening of psychotic symptoms (8, 9), (2) substance use emerges subsequent to psychosis as a consequence of neurobiological changes or as a coping strategy to alleviate symptoms (10, 11), (3) adverse childhood experiences are related to the later onset of both substance use and psychotic disorders (12), and (4) shared genetic liabilities underlie both psychotic spectrum disorders and substance use (13–15). Understanding potential associations between substance use and psychosis is complicated by the fact that associations may differ by substance use class or by poly-substance use.

Conceptually, psychotic disorders develop in stages, including a premorbid stage with subtle challenges in cognition and functioning (16), the clinical high risk (CHR) stage with subthreshold psychotic symptoms (17), the first episode of psychosis with onset of acute psychotic symptoms, and the residual phase that may include decreased symptom severity and frequency of acute psychotic episodes (18). While some research suggests that substance use contributes to the onset of psychosis (early psychosis, EP), a systematic review has documented more studies with null findings than studies with non-null results (4). Though researchers often examine the relationship between psychosis and substance use onset across all substance classes, a substantial proportion of studies focus specifically on cannabis use and psychotic disorder onset. Multiple studies indicate a correlative relationship between cannabis use and age of onset (8, 19–21), including evidence to suggest a dose-response relationship between levels of cannabis use and psychosis risk (22), though others report null findings (1).

While the evidence supporting the link between substance use and psychotic disorder onset has been mixed, the evidence supporting the link between substance use and greater psychotic symptom severity is more consistent. Baseline data of the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP), the NIH multisite trial that helped establish coordinated specialty care as the predominant model of care for early psychosis in the U.S. (23), support the association of substance use to more severe symptoms within individuals with early psychosis (24). Similar findings indicate cannabis use is associated with more severe symptoms (25, 26).

One major limitation of the existing literature on substance use and psychotic disorder associations is that it is based largely on epidemiological and clinical data from cross-sectional studies or longitudinal studies with a small number of measurements over months or years. Associations are either contemporaneous or between retrospectively classified substance use and symptom patterns. There are very limited intensive longitudinal data that examine patterns of substance use patterns and psychotic symptoms on a day-to-day or within-day basis, the time frame of expected bidirectional influence and strongest association. Thus, clinicians and researchers alike have limited understanding of the degree to which substance use may influence the day-to-day experiences of psychotic symptoms or vice versa.

Experience-sampling methodology (ESM) data may provide important insights into dynamic associations between substance use and psychotic symptoms. Methodologically, ESM has individuals track moment-to-moment symptoms (27, 28), an important sampling strategy considering the variable and episodic nature of psychotic disorders and substance use. Use of ESM designs may be particularly useful to evaluate the "self-medication hypothesis (29)" and the "reward deficiency syndrome (30)", theories that posit that youth in the high-risk or early stages of psychotic disorders use substances to attenuate emerging, and often brief or momentary, symptoms (10). However, previous ESM research is limited to two studies that examined cannabis associations in adult samples with psychotic disorders (31, 32). No ESM studies have assessed broader categories of substance use and symptom associations, particularly in an adolescent/young adult sample with CHR or EP.

To address this gap, we performed secondary analyses on ESM data from a study that examined the degree and temporal variability of affect, psychotic spectrum symptoms and thoughts of self-harm over the course of 21 days among youth at CHR

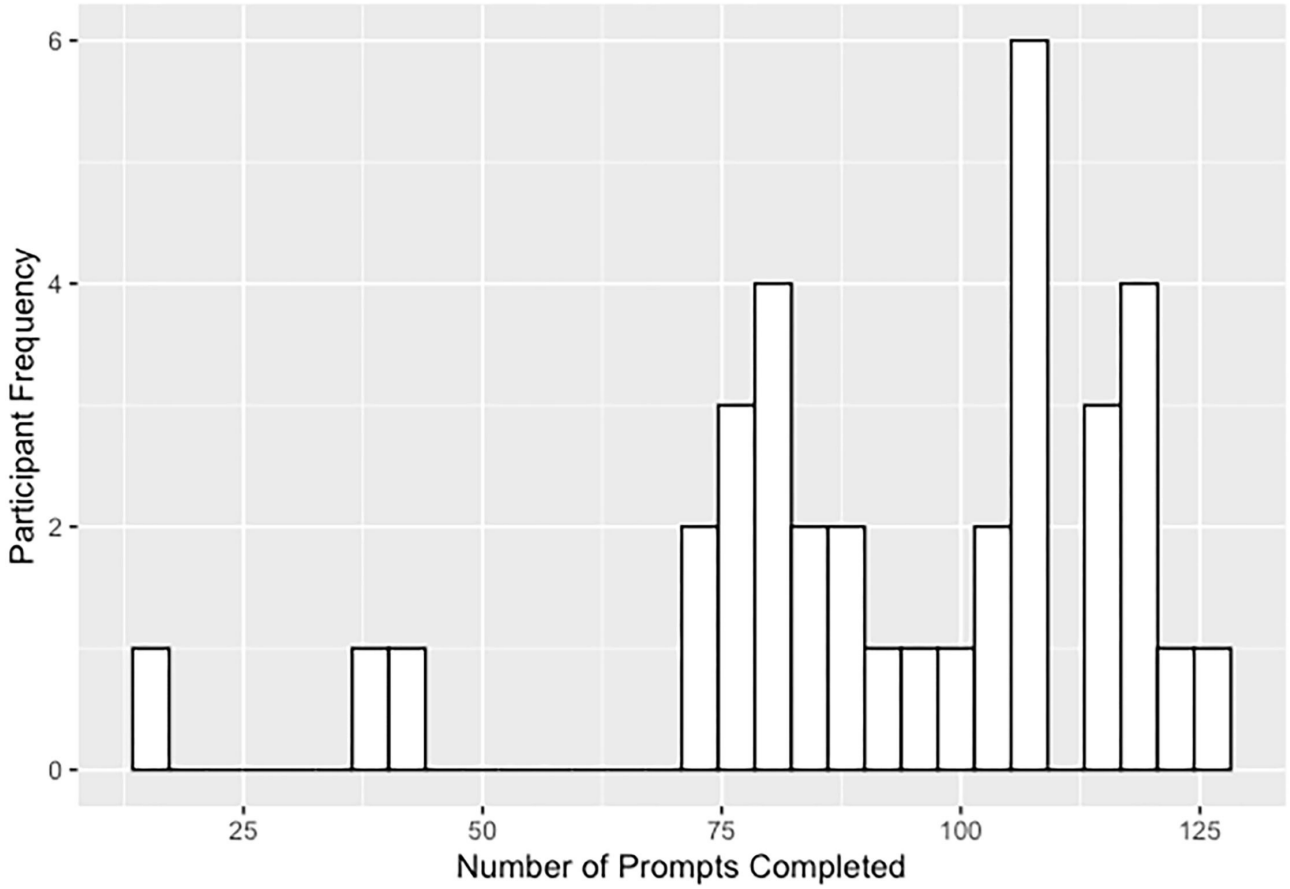

FIGURE 1 | Distribution of answered prompts for the 3-week ESM study including the 3 participants excluded due to low number of answered prompts.

for psychosis or with EP. The goals of these secondary analyses were to characterize substance use at a day-to-day and within-day level and explore the temporal within-person relationships between substance use, negative affect (NA), and psychosis.

METHODS

Participants

Experience-sampling data originated from a dataset of 69 participants including 36 individuals on the psychotic spectrum and 33 healthy controls. Data from 33 psychotic spectrum participants (51.5% CHR, 48.5% EP, including both affective and non-affective psychotic disorders) were included in the present study; three participants were excluded due to the low number of answered prompts (e.g., more than two standard deviations below the mean number of answered prompts; see **Figure 1**). Two participating sites at Maine Medical Center (MMC) and Beth Israel Deaconess Medical Center (BIDMC) recruited participants over a year and half. These sites have research and clinical programming and established referral networks for those with psychotic spectrum disorders. Eligible participants (1) were between the ages of 15 and 25, (2) spoke fluent English, (3) had an estimated IQ above 70, and (4) were willing and able to complete ESM procedures. Participants were ineligible if they had a current comorbid medical, neurological, or moderate to severe substance use disorder that would likely have a confounding impact on affect or psychotic symptoms. Baseline diagnostic assessments, conducted by trained clinician interviewers, determined if the participants met one of the following: (1) Criteria of Psychosis-Risk Syndromes (COPS) (within the 6 months prior to their participation) or currently meeting criteria for Attenuated Positive Symptom or Brief Intermittent Psychotic Syndromes, Persistent, based on the Structured Interview of Psychosis-Risk Syndromes [SIPS; Miller et al. (33)] or (2) criteria for a DSM-5 (34) psychotic-spectrum disorder, including schizophrenia-spectrum and mood disorders with psychotic symptoms but excluding substance-induced psychotic disorders.

Procedures

This multisite ESM study examined behavioral self-report data collected using the smartphone application MetricWire (www.metricwire.com), a HIPAA-compliant commercial service that sends surveys to participants' phones throughout the course of their daily lives. Institutional review boards at BIDMC and MMCRI approved study procedures. Research staff recruited participants using various forms of digital announcements

and flyers and by referrals from community partners. Written informed consent was obtained from all adult participants. Written consent of a legal guardian and written assent were obtained for participants under the age of 18. Study staff provided participants with an orientation to the MetricWire app and survey, with instructions on how to respond to surveys at 6-semi random prompts per day for 21 days. Staff instructed participants to respond to each survey prompt "in the moment" and to respond as soon as possible after receiving the prompt. Participants received six daily prompts, one per each 2-hour time block within a 12-hour window Pre-selected by the individual to be during typical waking hours (*e.g.*, 9am−9pm). Prompts were considered semi-random as participants received prompts at random times during each 2-hour time block in an effort to limit anticipatory responses. They were provided with a 15-minute window to respond to prompts. Participant remuneration was provided weekly for a minimum response rate of 50% and included weekly bonuses for high total responses, including extra bonuses for sustained compliance across all 3 weeks. Participants could earn up to $180 for the ESM component of the study.

Measures

Demographic information questionnaire. Collected information on the participant's age, sex at birth, gender, race, ethnicity, occupation, living arrangement, and the education and income of the participant and their legal guardian.

Diagnostic Assessments

Structured clinical interview of DSM-5 select Axis I & Axis II Disorders (*SCID-5RV, Research version)*; (34), is the leading interview for assessing disorders from the Diagnostic and Statistical Manual of Mental Disorders (35). The following modules were administered: Schizophrenia Spectrum, Bipolar, Substance-Related and Addictive Disorders, and Depressive Disorders. Anxiety and Trauma- and Stressor-Related sections were administered only upon relevant positive SCID-5RV screens. When applicable, staff secured written permission to communicate with family members to elicit additional information (observations and treatment, developmental, and family histories).

Structured Interview of Psychosis-Risk Syndromes [*SIPS, version 5.6;* Miller et al. (33, 36)], is one of two internationally accepted and validated interviews for assessing putatively prodromal symptoms and syndromes. Interviewers administered positive symptom queries to all participants who did not meet the criteria for a psychotic disorder.

Experience Sampling Methodology Variables

Substance use, NA, and psychotic symptom queries were embedded in a longer set of items asking participants about their momentary positive mood and social context. Instructions guided participants to answer each item relevant to the specific moment in which the phone prompt occurred to capture momentary rather than retrospective data. Only a small number of select items, including those about substance use, inquired about events since the last prompt, and these items were asked after momentary items to minimize the influence of retrospective thinking on momentary ratings.

Substance Use

Substance use was assessed at each prompt with one question: "Since the last beep [prompt], I have used/taken…" The participants were then given eight options, with examples, to select including: Depressants (ex. alcohol, xanax, klonopin, ativan), Stimulant or Caffeine, Sedatives (allergy or sleep medicine, oxycontin), Psychedelics (ex. LSD, ecstasy), Nicotine (ex. cigarettes, tobacco, or vaporizers), Cannabis, Other, and Nothing. Staff staff instructed participants to include prescription and over-the-counter medications or substances as well as illicit substances for the given classes. One item, "In the past 24 hours, did you take your prescribed medications" was included during the first answered prompt of the day with the following responses: "All, as prescribed", "Yes, but not all as prescribed", "No", and "I have no prescription medications".

Negative Affect

Negative affect (NA) was measured by responses to 6 items, each beginning with the stem "I feel" and followed by descriptors ("irritable", "lonely", "down", "insecure", "guilty", "stressed") (37). These were interspersed with 3 items assessing positive affect ("happy", "relaxed", "content"). Participants reported how strongly they felt each emotion at that moment based on a 7-point Likert scale from 1 ("Not at all") to 7 ("Very much"). Momentary NA was calculated as the mean response for all 6 items answered at each prompt. The 6-item NA scale showed satisfactory within-person and between person reliability ($\omega = 0.73$, $\omega = 0.93$, respectively). To account for between-person variability on mean levels of NA, deviations from the individual's person-centered mean over the course of the study were used in exploratory modeling (38).

Psychotic Symptoms

Psychotic symptoms were evaluated by responses to 9 items: "I feel suspicious", "I can't let go of my thoughts", "My thoughts are influenced by other people", "I feel unreal", "I see things that other people can't see", "I hear things that other people can't hear", "I feel like I am losing control (of my thoughts)", "It's hard to express my thoughts in words", and "My thoughts are so loud it's as if I can hear them" (37). These responses reported the degree to which the participants experienced each item at the moment of the prompt. Responses were recorded on 7-point Likert scale from 1 ("Not at all") to 7 ("Very much"). Momentary psychotic symptoms was calculated as the mean response for all 9 items answered at each prompt. The 9-item scale showed satisfactory within-person and between-person reliability ($\omega = 0.78$, $\omega = 0.96$, respectively). To account for between-person variability on mean levels of psychotic symptoms, deviations from the individual's person-centered mean over the course of the study were used in exploratory modeling (38).

Statistical Analysis

We categorized a participant as having recurrent substance use (RSU) if they indicated substance use during at least 5% or more answered prompts. In determining recurrent substance use, means and standard deviations for each substance class were examined for participants who indicated use for a specific substance class during 2 or more prompts. After

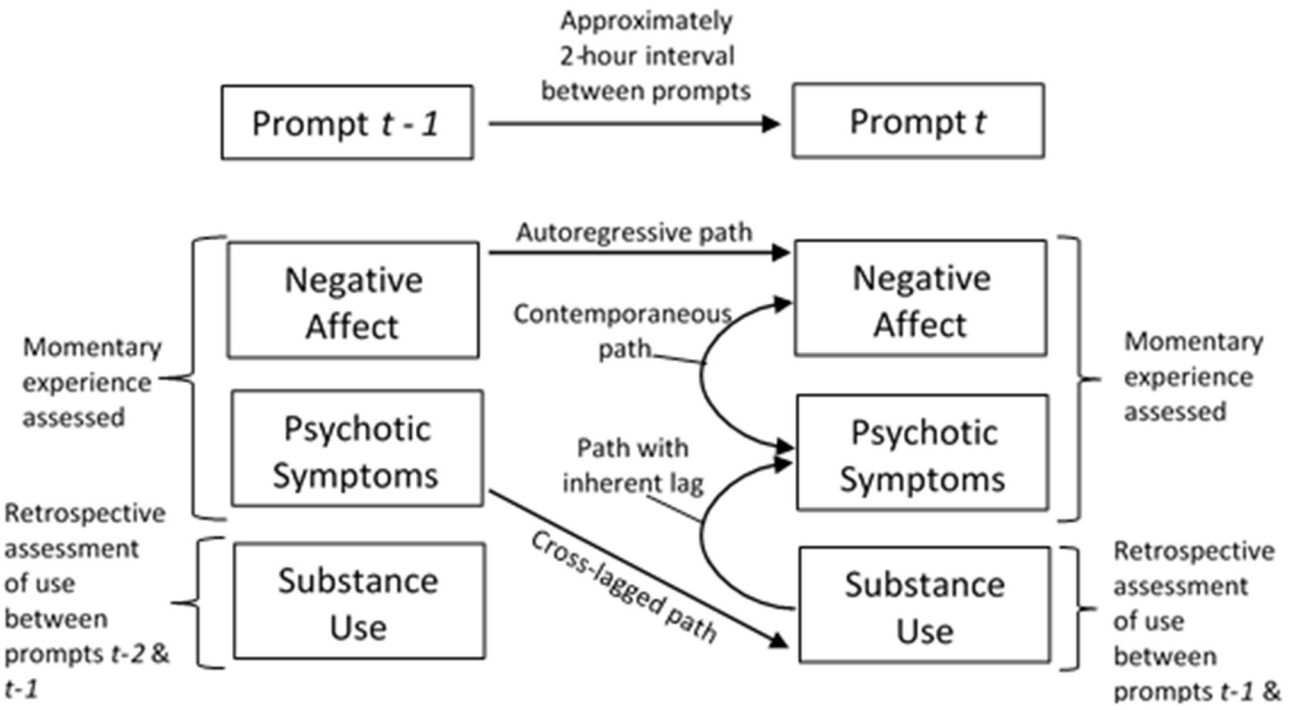

FIGURE 2 | Experience sampling methodology with multilevel vector autoregressive (MVAR) estimation of autoregressive, cross-lagged, and contemporaneous paths.

examining the lowest values within one standard deviation of the mean for each substance use class, the 5% of prompts cutoff was selected as the standard to separate infrequent or occasional use from RSU across all substance use classes. Descriptive data and summary statistics (39) were used to characterize the rate of RSU in each substance class, the percent of prompts reflecting use, and the frequency of use across multiple classes. Diagnostic group differences (*i.e.*, CHR and EP) were evaluated via chi-square tests for categorical variables and *t*-tests for continuous variables and *post hoc* power analyses were conducted with G*Power Version 3.1 (40). Visualizations of prompts and substance use frequencies were created using the package "ggplot2" (41) and "plotly"(42) in R version 3.6. Within-person and between-person reliability omega coefficients were calculated using the R package "multilevelTools" (43).

Exploratory multilevel vector autoregressive (MVAR) models estimated within the dynamic structural equation modeling framework in Mplus 8.3 (44) used person-centered means of psychotic symptoms and NA in addition to a binary substance use indicator variable (any class of substance). MVAR were used in the analyses of ESM data as these models can accommodate the two-level structure of ESM data, the use of multiple outcomes, and estimation of contemporaneous (*i.e.*, 0-lag) *and* lagged relationships, which measure the extent that a symptom at timepoint (*i.e.*, prompt) *t*-1 predicts itself at timepoint *t* (38). For the current study, we were particularly interested in whether substance use influenced deviations from participants' person-centered means of psychotic symptoms and/or NA. Cross-lagged and contemporaneous regression paths provide an indication of whether substance use exacerbates or reduces one's experience of psychotic symptoms and negative affect at the previous prompt or at the current prompt, respectively **(Figure 2)**. Given the retrospective manner in which the substance use question was asked (e.g., "Since the last prompt…"), there is a lag embedded in what would otherwise be considered a contemporaneous path between substance use and psychotic symptoms or NA. Parameter estimates were considered to be significant if the 95% credible interval did not include 0. The MVAR model allowed within-person residuals to vary across individuals; the log of residual variances was estimated to ensure that all residual variances are positive.

The MVAR model was limited to analysis of substance use (any class) rather than specific substance use classes due to sample size limitations for multi-level modeling. In recognizing that substance use associations to psychotic symptoms and NA may vary the individual or substance use class, we estimated individual autoregressive (1) lag models for each participant who indicated substance use. These were conducted to assess whether between substance use associations to psychotic symptoms and negative affect varied from the within-person associations estimated in the MVAR model. For both sets of models, time was transformed into discrete 2-hour intervals to accommodate existing ESM procedures (semi-random prompts delivered during 6 2-hour blocks) using the "TINTERVAL" function in Mplus. This was performed to allow for the unequal spacing between measurements

TABLE 1 | Demographic characteristics for participants with N (%) reported unless otherwise noted.

	CHR	EP	Total sample
CHR	17 (100)	0 (0)	17 (51.5)
EP	0 (0)	16 (100)	16 (48.5)
Age, mean (SD), range	19.53 (2.9), 16–24	19.63 (2.3), 16–24	19.58 (2.6), 16–24
Sex assigned at birth			
Male	7 (41.2)	9 (56.3)	16 (48.5)
Female	10 (58.8)	7 (43.8)	17 (51.5)
Gender			
Male	4 (23.5)	8 (50.0)	12 (36.4)
Female	7 (41.2)	6 (37.5)	13 (39.4)
Trans male/Trans man	2 (11.8)	0 (0)	2 (6.1)
Trans female/Trans woman	2 (11.8)	1 (6.3)	3 (9.1)
Genderqueer/Gender non-conforming	2 (11.8)	1 (6.3)	3 (9.1)
Race and ethnicity			
White	14 (82.4)	10 (62.5)	24 (72.7)
Hispanic/Latin	2 (11.8)	1 (6.3)	3 (9.1)
Black	1 (5.9)	2 (12.5)	3 (9.1)
Interracial	0 (0)	1 (6.3)	2 (6.1)
Other	2 (11.8)	2 (12.5)	4 (12.1)
Occupation and education			
Years of education, mean (SD), range	12.4 (2.6), 10–17	12.2 (1.9), 7–15	12.7 (2.3), 7–17
Student	14 (82.4)	12 (75)	26 (78.8)
Worked full time	4 (23.5)	0 (0)	4 (12.1)
Worked part time	4 (23.5)	6 (37.5)	10 (30.3)
Worked within the last year	4 (23.5)	4 (25)	8 (24.2)
Did not work within the last year	5 (29.4)	6 (37.5)	11 (33.3)
Parent's education			
No schooling	0 (0)	1 (3.1)	1 (1.5)
Some high school	2 (5.9)	1 (3.1)	3 (4.6)
Completed high school	9 (26.5)	0 (0)	9 (13.8)
Some college/technical school	6 (17.7)	7 (21.9)	13 (20.0)
Completed college/technical school	6 (17.7)	13 (40.6)	19 (29.2)
Some graduate/professional school	2 (5.9)	0 (0)	2 (3.1)
Completed graduate/professional school	9 (26.5)	9 (28.1)	18 (27.7)
Living arrangement			
With family	12 (70.6)	13 (81.3)	25 (75.8)
On own in apartment/dorm	4 (23.5)	1 (6.3)	5 (15.2)
With other(s)	0 (0)	2 (1.3)	2 (6.1)
Other	1 (5.9)	0 (0)	1 (3.0)
Income			
< $20,000	3 (17.6)	2 (12.5)	5 (15.2)
$20,000 – $39,999	0 (0)	2 (12.5)	2 (6.1)
$40,000 – $59,999	1 (5.9)	1 (6.3)	2 (6.1)
$60,000 – $99,999	4 (23.5)	1 (6.3)	5 (15.2)
$100,000 or more	2 (11.8)	4 (25)	6 (18.2)
No response/unknown	7 (41.2)	6 (37.5)	13 (39.4)

CHR, Clinical High Risk; EP, Early Psychosis.

that naturally occur between days (e.g., accounting for non-measurement intervals that occur during sleep) and for days in which fewer than 6 prompts were answered (45). Mplus code for all models can be found: https://osf.io/gnrz7/.

RESULTS

Among the 33 participants (see **Table 1** for demographic characteristics) included in the analyses, SCID interviews identified 13 (39.4%) that met criteria for a current or lifetime

TABLE 2 | Rate of recurrent substance use with experience sampling data characteristics by CHR and EP groups with *N* (%) reported unless otherwise noted.

	CHR ***n = 17***	**EP** ***n = 16***	***p*-value**	**Total sample** ***n = 33***
Number of valid reports [mean (SD) range]	99.1 (14.5) 72–127	97.9 (19.4) 72–117	0.85	98.5 (16.8) 71–127
RSU any class	14 (82.4)	13 (81.3)	0.93	27 (81.8)
% of prompts that indicate any substance use	44.0	52.1		47.7
RSU Nicotine	5 (29.4)	4 (25.0)	0.78	9 (27.3)
% of prompts that indicate nicotine use	70.8	78.4		74.2
RSU stimulant	8 (47.1)	7 (43.8)	0.85	15 (45.5)
% of prompts that indicate stimulant use	24.6	19.7		23.6
RSU cannabis	2 (11.8)	4 (25.0)	0.32	6 (18.2)
% of prompts that indicate cannabis use	47.4	34.9		39.1
RSU depressant	1 (5.9)	3 (18.8)	0.26	4 (12.1)
% of prompts that indicate depressant use	33.7	15.6		20.1
RSU other	4 (23.5)	1 (6.3)	0.17	5 (15.2)
% of prompts that indicate sedative/other use	26.8	23.6		26.2
RSU One substance class	9 (52.9)	6 (37.8)	0.37	15 (45.5)
% of prompts that indicate any substance use	31.9	40.5		35.3
RSU two or more substance classes	5 (29.4)	6 (37.5)	0.62	11 (33.3)
% of prompts that indicate any substance use	65.9	64.8		65.2
RSU three or more substance classes	4 (23.5)	1 (6.3)	0.17	5 (15.1)
% of prompts that indicate any substance use	72.2	95.3		76.8
Indicated prescription medications	13 (76.5)	15 (93.8)	0.16	28 (84.8)
Indicated medication adherence (≥90% of days)	7 (53.8)	12 (80.0)	0.14	19 (67.9)
NA [mean (SD) range]	3.0 (1.2) 1.1–5.6	2.3 (1.1) 1.1–4.1	0.07	2.7 (1.2) 1.1–5.6
PA [mean (SD) range]	3.5 (1.1) 1.3–5.0	4.2 (1.2) 2.2–6.7	0.09	3.9 (1.2) 1.3–6.7
PSY [mean (SD) range]	2.3 (1.3) 1.0–6.3	1.8 (1.0) 1.0–4.0	0.20	2.1 (1.2) 1.0–6.3

CHR, Clinical High Risk; EP, Early Psychosis; NA, Negative Affect; PA, Positive Affect; PSY, Psychotic Symptoms; RSU, Recurrent Substance Use.
p value reported for Chi square (categorical variables) and t-tests (continuous variables) comparing EP and CHR groups.

substance use disorder with 4 (12.1%) indicating a lifetime cannabis use disorder, 6 (18.2%) a current cannabis use disorder, 1 (3.0%) a lifetime sedative use disorder, 1 (3.0%) a lifetime stimulant use disorder, and 1 (3.0%) with multiple substance use disorders (cannabis, opioid, stimulant). Data show high rates of compliance to semi-random prompts across CHR ($M = 99.1$ [78.6% of possible prompts], $SD = 14.5$) and EP ($M = 97.9$ [77.7% of possible prompts], $SD = 19.4$) participants. Using ESM data, most participants ($N = 30$, 90.9%) indicated substance use at one prompt or more during the 3-week data collection window; only 3 participants (9.1%) did not indicate any momentary substance use. The majority of participants ($N = 27$, 81.8%) were categorized as having RSU **(Table 2)**. The most common substances included stimulants/caffeine ($N = 15$, 45.5%), products containing nicotine ($N = 9$, 27.3%), depressants ($N = 4$, 12.1%), and cannabis ($N = 6$, 18.2%). No participants indicated use of psychedelics and one participant (3.0%) indicated RSU of sedatives, which was subsequently recoded into the other category, which included four other participants (12.1%) who indicated RSU. Additionally, participants with RSU indicated substance use at ∼48% of answered prompts. Substance use patterns reflected pervasive and consistent use for participants with RSU of nicotine (∼74% of answered prompts) and moderate for participants with RSU of cannabis (∼39% of answered prompts). Visualizations of momentary substance use reflected the percentage of answered prompts by each substance use category, including prompts when multiple substance classes were indicated **(Figure 3)**.

Approximately half of the participants with RSU indicated use that was limited to a single substance class ($N = 14$, 55.6%). For the remaining participants with RSU, six (22.2%) specified recurrent use for two classes of substances while five participants (18.5%) indicated recurrent use for three or more classes of substances. Visualizations of momentary substance use reflected the proportion of answered prompts with no use, single substance class use, and multiple substance class use **(Figure 4)**. Most participants responded that they were prescribed medication ($N = 28$, 84.8%) with a majority of these individuals indicating that they were adherent at least 90% of the time ($N = 19$, 67.9%). There were no significant differences between the CHR and EP participants for number of answered prompts, rates of RSU, or mean momentary symptom ratings **(Table 2)**. CHR participants showed a trend of higher mean NA ratings ($t = 1.9$, $p = 0.07$) over the 3-week ESM window compared to EP participants. Chi-square and *t*-tests did not achieve appropriate power (0.34–0.54) for observed effect sizes.

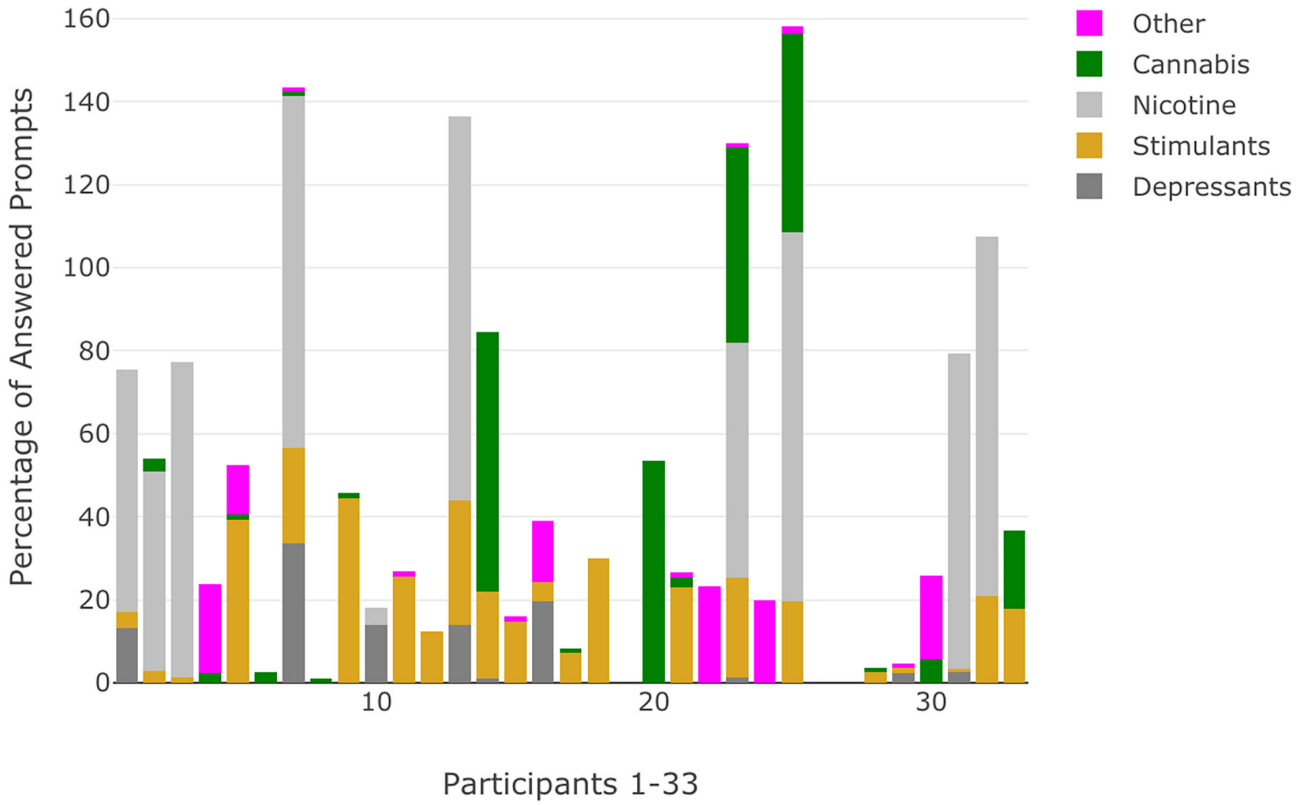

FIGURE 3 | Percentage of answered prompts that indicate substance use categorized by substance use class for each participant. Percentages that exceed 100 reflect participants who indicated use of substances across multiple classes at the same prompt.

MVAR Model Results

Table 3 provides the posterior median parameter estimates for the MVAR model of substance use (any class), psychotic symptoms, and NA. Results indicated significant autoregressive relationships for NA ($\beta = 0.33$, 95% CI: 0.25, 0.41) and psychotic symptoms ($\beta = 0.39$, CI: 0.28, 0.49) such that deviations from the person-centered mean at *t-1* predict deviations in the same direction for the subsequent timepoint *t*. Model estimates showed no significant associations between substance use and lagged psychotic symptoms ($\beta = 0.02$, CI: −0.01, 0.05), nor with psychotic symptoms ($\beta = 0.01$, CI: −0.02, 0.05), or NA ($\beta = -0.02$, CI: −0.07, 0.04) at prompt *t*. However, substance use was associated with lagged NA ($\beta = -0.02$, CI: −0.05, <-0.00) such that participants who indicated that they had used substances since the previous prompt (e.g., interval between prompt *t-1* and prompt *t*) had experienced lower NA at the previous prompt.

When considering the variances (intercepts) of person-specific means over time for each symptom, individuals exhibited more variability around their person-centered mean of NA compared to the variability around their person-centered mean of psychotic symptoms. These estimates were small relative to random effect variances estimates, which suggest the way an individual's momentary responses fluctuate around their person-centered mean are not considerably different across people. In contrast, random effect variances estimates of NA ($\alpha = 0.83$), psychotic symptoms ($\alpha = 3.37$), and substance use ($\alpha = 2.53$) indicated that there are likely distinct differences across people in regards to the way each respective symptom can be explained from the autoregressive and cross-lagged paths estimated in the MVAR model.

The between-level variances for NA and psychotic symptom autoregressive paths had credible intervals of [0.03, 0.10] and [0.05, 0.14], respectively, which suggest that the degree to which psychotic symptoms and NA at prompt *t-1* are associated with psychotic symptoms and NA, respectively, at prompt *t* varies across people. Conversely, the between-level variances for most inter-symptom paths (e.g., substance use associations between lagged or contemporaneous psychotic symptoms/negative affect) had credible intervals between [0.00, 0.01] which suggests little variability across people; the credible interval remained positive as Mplus does not allow negative values. The exceptions included the path between negative affect and lagged psychotic symptoms with a credible interval of [0.03, 0.18] and the contemporaneous path between negative affect and psychotic symptoms [0.11, 0.49]. These variance estimates suggested that there was between-person variability in regards to the degree momentary psychotic symptoms at prompt *t-1* were associated with momentary NA at the subsequent timepoint, prompt *t* and also to the degree negative affect was associated with psychotic symptoms at prompt *t*.

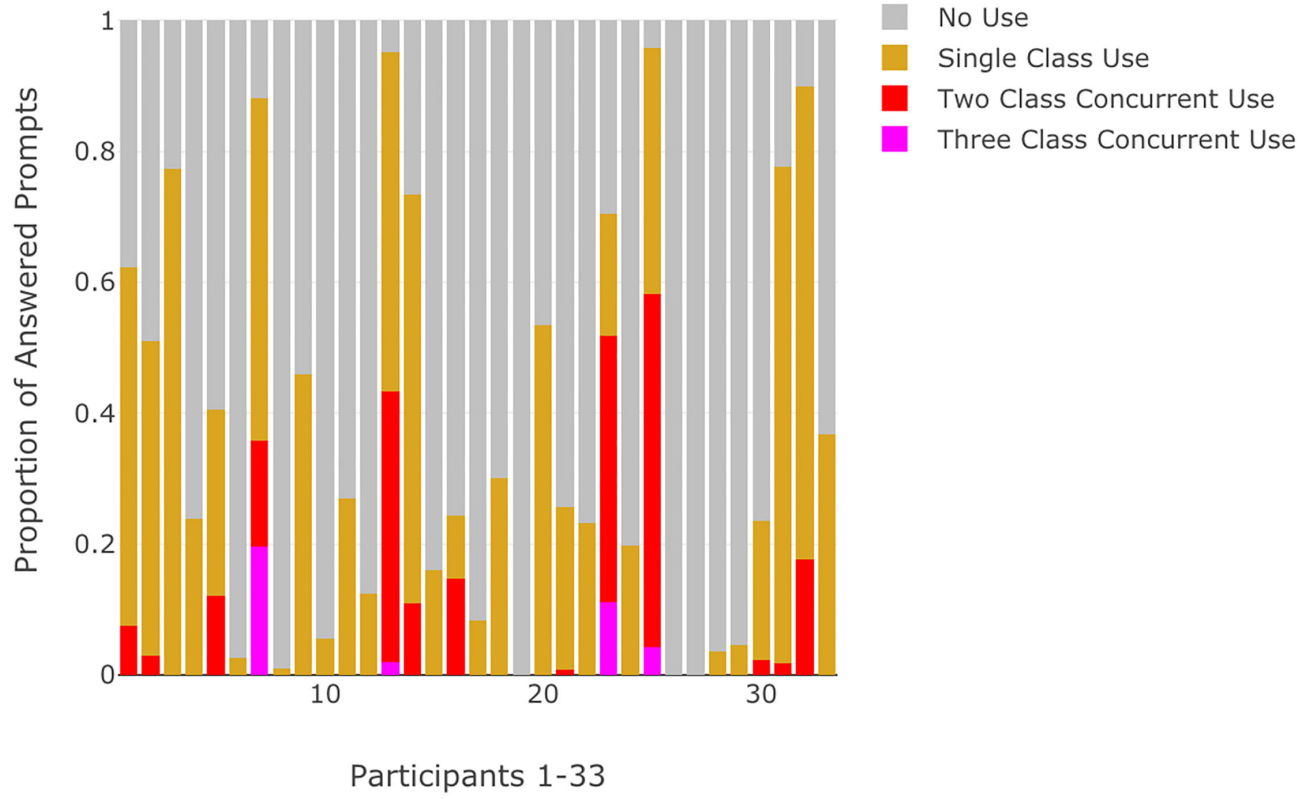

FIGURE 4 | Proportion of answered prompts categorized by no use, single substance class use, or multiple concurrent substance use for each participant.

N = 1 Autoregressive (1) Lag Models

Individual autoregressive lag models were estimated for 29 participants, who indicated substance use during at least one answered prompt (an additional participant was excluded due to no variation in psychotic symptoms). Person-level MVAR model diagrams with significant parameters and corresponding credible intervals can be found for each participant within Supplementary Materials (https://osf.io/gnrz7/). Person-level models reflected variable symptom relationships. Of the 29 person-level models estimated, 3 (10.3%) indicated significant substance use and psychotic symptom paths that were not detected in the MVAR model (Participants 2, 7, 30 in Supplementary Materials). All three participants had RSU with nicotine with one of the participants indicating polysubstance use with additional RSU of depressants and stimulant classes. Two (6.9%) person-level models indicated a significant lagged, positive association between substance use and psychotic symptoms. This suggests that higher levels of momentary psychotic symptoms at prompt *t-1* were associated with subsequent substance use that occurred between prompt *t-1* and *t*. Two (6.9%) person-level models indicated a significant positive association between substance use and psychotic symptoms, which indicates that these participants were more likely to exhibit greater levels of psychotic symptoms at prompts when substance use was indicated in the interval between prompt *t-1* and prompt *t*.

DISCUSSION

The relationship of substance use, including medications and over-the-counter products, to psychotic and mood symptoms during the emergence of schizophrenia and other psychotic-spectrum disorders is complex. Yet understanding this relationship is essential for diagnostic and treatment decision-making, public policy, and systems of service delivery. Much of what is known comes from retrospective self-report or prospective clinician ratings at one or, perhaps, several points over the course of months or years. Less is known about substance use patterns and their potential associations with psychotic and mood symptoms within the daily lives of these adolescents and young adults. The ESM data from individuals with CHR and EP that are reported here provide a new window into these day-to-day patterns with the hope that they can inform the targets and timing of interventions designed to interrupt progression of both substance misuse and serious mental health symptoms.

As expected, a majority of the sample (90.9%) reported use of substances, including illicit, over-the-counter, and medications falling within the selected classes. A majority (n = 27, 81.8%) of this sample were characterized as having RSU, defined as substance use occurring during at least 5% of answered prompts. For this group as a whole, 48% of answered prompts reflected

TABLE 3 | Posterior median parameter estimates with 95% credible intervals for MVAR model of substance use, psychotic symptoms, and negative affect.

Parameter	Estimate	95% Credible interval
Intercepts		
Intercept (NA)	<-0.01	[−0.03, 0.02]
Intercept (PSY)	<-0.00	[−0.02, 0.02]
Intercept (SU)	**0.35**	**[0.24, 0.47]**
Ln Var NA	**−1.25**	**[−1.57, −0.94]**
Ln Var PSY	**−2.31**	**[−2.94, −1.68]**
Ln Var SU	**−2.56**	**[−3.12, −2.00]**
Regression path intercepts		
Autoregressive NA	**0.33**	**[0.25, 0.41]**
Autoregressive PSY	**0.39**	**[0.28, 0.49]**
SU on NA	−0.02	[−0.07, 0.04]
SU on Lag NA	**−0.02**	**[−0.05, <-0.00]**
SU on PSY	0.01	[−0.02, 0.05]
SU on lag PSY	0.02	[−0.01, 0.05]
NA on lag PSY	−0.09	[−0.23, 0.02]
PSY on lag NA	**0.03**	**[0.01, 0.06]**
NA on PSY	**0.64**	**[0.46, 0.84]**
Between–person residual variances		
Intercept NA	<0.01	[<0.01, <0.01]
Intercept PSY	<0.01	[<0.01, <0.01]
Intercept SU	**0.10**	**[0.07, 0.18]**
Autoregressive NA	**0.05**	**[0.03, 0.09]**
Autoregressive PSY	**0.07**	**[0.04, 0.13]**
SU on NA	<0.01	[<0.01, 0.01]
SU on lag NA	<0.01	[<0.01, <0.01]
SU on PSY	<0.01	[<0.01, 0.01]
SU on lag PSY	<0.01	[<0.01, 0.01]
NA on lag PSY	**0.07**	**[0.03, 0.16]**
PSY on NA lag	<0.01	[<0.01, 0.01]
NA on PSY	**0.23**	**[0.11, 0.49]**
Variance NA	**0.83**	**[0.52, 1.41]**
Variance PSY	**3.37**	**[2.18, 5.88]**
Variance SU	**2.53**	**[1.60, 4.35]**

NA, Negative Affect; PSY, Psychotic Symptoms; SU, Substance Use; Ln Var, Natural log of variance estimate; lag, lagged response at prompt t-1.
Bold indicates significant parameters.

consistent momentary use of substances, with those who used nicotine ($n = 9$, 27.3%) and cannabis ($n = 6$, 18.2%) reporting high and moderate frequencies of use (74 and 39% of answered prompts, respectively). Stimulant use (which included caffeine) was the most commonly reported RSU class ($n = 15$, 45.5%), but ESM data reflected less consistent use (23.6% of answered prompts) relative to nicotine and cannabis use. Although rates of use align with previously reported clinical and epidemiological data for CHR and EP samples, these ESM data provide an initial look into the frequency of substance use at the momentary level. No differences were observed between diagnostic groups for RSU rate or momentary mean of NA or psychotic symptoms, but these comparisons were not adequately powered, rendering this finding unreliable.

Given the frequency of momentary substance use observed within this sample, MVAR models were estimated to examine whether substance use was related to lagged or subsequent deviations from person-centered means of psychotic symptoms and NA. We anticipated increased NA to precede substance use and both increased NA and substance use to precede increased psychotic symptoms, consistent with the concept of self-medication. To our surprise, parameter estimates suggested that *lower* levels of NA were associated with subsequent substance use. Although all classes of substances (including prescription medications) are combined into the substance use variable, creating the real possibility that effects cancel each other out, this finding does not support a general theory of self-medication. One possible explanation may be that individuals with CHR or EP engage in substance use when they are in situations (e.g., with peers) that are more positive and less negative. They may also use in an effort to *maintain* lower momentary experiences of NA that occur prior to substance use.

Contrary to a previous ESM study which indicated that cannabis use resulted in increases in hallucinations and decreases in negative affect (31), no significant within-person associations were observed between substance use and subsequent psychotic symptoms. Differences in findings may be due to the current's study design aggregating momentary ratings of nine psychotic symptom items that include both hallucinations and delusions. Inter-symptom relationships may vary based on the specific type of psychotic symptom (hallucinations vs. delusions). Prior work has also noted that potency may moderate cannabis associations to psychosis incidence (46), psychotic episode relapses (47), and positive symptoms (48). Future studies should assess quantity and potency of specific substances and their lifetime use to determine if these factors may moderate experiences of NA or psychotic symptoms in individuals with CHR or EP. Additionally, sample size constraints in the current study limited MVAR variable selection and analysis of specific drug class use. A sensitivity analysis limited to individuals with RSU of nicotine and/or cannabis use (i.e., the two most frequently used substances) indicated a stronger association between nicotine/cannabis use and lagged NA ($\beta = 0.12$, CI: −0.20, −0.05). No new significant associations were observed (see Sensitivity Analysis Table at: https://osf.io/gnrz7/).

Furthermore, current study findings differed from previous between-person analyses that have found substance use to be associated with higher levels of psychotic symptoms. While current results may be attenuated by the small sample size, previous work has suggested that within-person associations between cannabis and psychotic symptoms may differ from between-person associations that may be observed longitudinally (21). An important consideration in understanding the mixed findings observed in clinical and epidemiological data, and another advantage of ESM data, is the degree to which there is between-person variability in within-person associations over time (person-level analyses). For one individual, substance use may exacerbate psychotic symptoms while for another, substances may be used as a coping strategy. In the current study,

three individual autoregressive lag models indicated positive associations between substance use and psychotic symptoms that were not significant in the MVAR model. While these statistical approaches need to be validated, this type of ideographic analysis is likely to be more useful to personalizing early intervention strategies and to research that disentangles the nature of these relationships.

Of course, the descriptive and exploratory findings must be considered within the context of study limitations. This ESM study was not specifically designed to test associations between substance use and psychotic symptoms and NA; dynamic analyses were exploratory. Individuals with severe substance use expected to interfere with the accurate assessment of other variables were excluded. The small sample and collection of binary data on substances by class restrict our ability to fully understand the day-to-day patterns of specific substance use or disentangle relationships between symptoms and medication, over-the-counter, and illicit substances. In particular, the stimulant class included a combination of legal substances (*e.g.*, caffeine products), prescription medications (*e.g.*, Adderall), and illicit substances (*e.g.*, cocaine). Future work may include multiple questions or non-binary items to assess substance use and include items assessing cravings and the quantity/potency of substances used, or examining use in larger and more homogeneous samples (e.g., only CHR or EP, adolescent or adult).

The MVAR model examined substance use associations across all classes of substance use. These associations are likely multifactorial and expected to differ not only by the specific substance class and specific substance but also by means of ingestion, dose, and potency. Additionally, while analyses accounted for missing data, including non-measurement intervals that occur between response days with fixed interval spacing (2-hours), actual interval spacing between adjacent prompts varied between 1 and 240 min. Modeling of time is an important consideration for ESM studies of substance use, considering that substances differ in terms of pharmacokinetics (i.e., the duration of a specific substance effect) (49). To control for the timing of substance intake, future ESM studies may utilize event-contingent sampling whereby prompts are answered after each instance of substance use (50, 51) in contrast to the semi-random time sampling procedures used in the current study. Finally, analyses are limited to the 3-week ESM data collection window; missing patterns of use and symptom-substance relations that vary episodically or during an acute episode may not have been captured during the study.

Despite these limitations, these data provide new information on the frequency of momentary substance use across important classes of substances, over a meaningful period of time, and in a sample for which properly targeted interventions may have long-lasting effects. Associations between substance use and psychosis differ from common theories that substance use during the course of emerging psychosis is primarily a means of self-medication or that entire classes of substances exacerbate psychosis. However, given the impracticality of truly experimental designs (randomizing individuals to use or not use substances at specific intervals in real life), the analyses demonstrate the potential of statistical modeling of ESM data to increase our understanding of the dynamic substance use and symptom relationships within individuals and across the emergence of and recovery from psychotic disorders. Within-person associations are likely to vary on an individual level, by substance, and over time. Understanding individual patterns over time may be key to disrupting the progression of pathology.

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 Maine Medical Center Research Institute Beth Israel Deaconess Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DW and EB drafted the manuscript. KW, RM-G, KE, KJ, KP, and DR critically revised the manuscript. KW, DR, and KP contributed to study conception and design. DW, EB, KW, RM-G, KE, KJ, KP, and DR contributed to acquisition, analysis, and interpretation of data. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Dropout Rates in Psychosocial Interventions for People With Both Severe Mental Illness and Substance Misuse: A Systematic Review and Meta-Analysis

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Introduction: Over the years, many psychosocial interventions for individual having both a psychotic spectrum disorder and a substance use disorder diagnoses have been developed and studied. However, there is a high dropout rate among this clinical population.

Objectives: This meta-analysis aims to replicate a previous meta-analysis on the effects of psychosocial treatment for dual disorders, while including and determining the dropout rates in those type of interventions.

Method: Based on a Cochrane systematic review conducted in 2019, we conducted a meta-analysis including 40 randomized clinical trials on psychosocial treatment among persons suffering from schizophrenia spectrum disorder and substance use disorder.

Results: A dropout rate of 27,2% was obtained. Stimulants use significantly affected dropout rates. Age, gender, diagnosis, alcohol and cannabis abuse, and duration of treatment did not affect dropout rates.

Conclusion: The 27,2% rate of dropout from psychosocial treatment highlights the need to engage participants having a dual diagnosis from the start by focusing on therapeutic alliance and motivation for treatment.

Keywords: dropout, psychosocial interventions, severe mental illness, psychotic spectrum disorder, substance use disorder, dual diagnosis

INTRODUCTION

Severe mental disorders are defined by the nature of the diagnosis, the degree of disability and the duration of the disorder (1). As such, the following diagnoses are considered severe mental disorders: schizophrenia and related disorders, bipolar disorders, and severe depressive disorders (2–6). Approximately 40–60% of individuals with a serious mental disorder also present with a comorbid substance use disorder (7–9). For individuals with schizophrenia, the risk of comorbid alcohol misuse is three times more likely, whereas the risk for drugs misuse is six times more likely

(10), when compared to people without a psychiatric disorder. Overall, people with schizophrenia are 5.3 times at greater risk to present with a substance use disorder than the general population (11). In fact, the proportion of individuals with schizophrenia who present with a substance use disorder is significantly higher than what is found in most other clinical or non-clinical populations (7, 9, 12–14).

It is important to note that severe mental disorders come with a variety of challenges (15), and these are exacerbated with substance misuse, namely isolation, anxiety, depression, suicidal thoughts, behavioral and emotional problems (2). Even mild substance abuse is associated with increased risk for suicide, AIDS, hepatitis, assault, incarceration, homelessness, and fewer social and financial resources (4, 16). Furthermore, substance abuse in severe mental disorders interferes with diagnostic and treatment and causes a multitude of difficulties in a clinical population already facing major difficulties (14, 17).

Over the years, many psychosocial interventions have been developed specifically for this dual diagnosis population. These include interventions and programs such as motivational interviewing (MI), cognitive behavioral therapy (CBT), contingency management (CM), psychoeducation, integrated treatments (IT), psychosocial treatment, and assertive community treatment (4, 18–20). However, people with comorbid severe mental disorders and substance misuse have been described as particularly vulnerable to treatment dropout (21). Ensuring treatment adherence is a major issue in psychiatry, as well as in general medical practice (22). Why are individuals with comorbid severe mental and substance use disorders at higher risk of treatment dropout? In their review on the subject, Kreyenbuhl et al. (23) reported that younger age, male gender, lack of insight, a tendency to minimize symptoms and their impact, and low social functioning as well as a low socioeconomic status was linked to drop out rates. Of the most cited reasons for disengaging is the desire to solve problems on their own (23), dissatisfaction with the treatment or the impression that it wouldn't help, feeling that they already had improved, feeling that they were too unwell, and medication and its side-effects. Other reasons mentioned were having forgotten the appointment and a fear of the mental health system due to previous negative experiences (23). Treatment willingness and engagement can also be influenced by the therapeutic alliance with the therapist, perceived accessibility of care and the client's belief that the treatment will help (24). This is even more an issue for individuals with concurrent substance abuse disorder and/or addiction, with high drop-out rates across treatments (21). Dropping out of psychosocial treatments is associated with a number of clinical, social and economic consequences, as well as higher risk of relapse, re-hospitalization and poorer prognosis. A previous meta-analysis from our team (25) on the drop-out rates from psychosocial treatments among individuals with a psychotic disorder indicated that ∼13% (of the 4,374 participants) dropped out prior to, or during, the treatment. Similar dropout rates have been found by Bighelli et al. (26). The authors suggest that these results may be an underestimation of the actual dropout rate due to publication bias in favor of studies presenting lower drop-out rates, as well as the exclusion

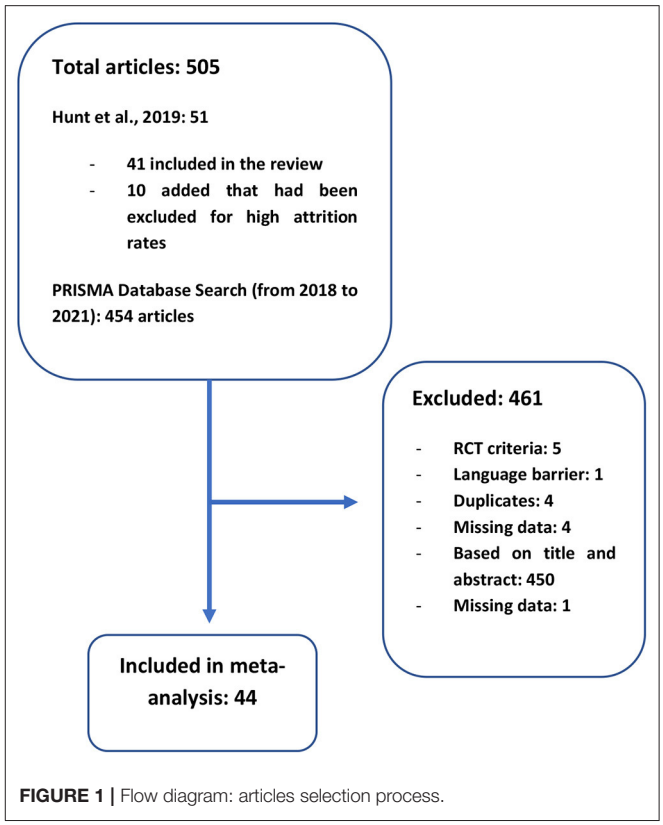

FIGURE 1 | Flow diagram: articles selection process.

from the meta-analysis of trials involving patients with psychosis and substance use disorders. This meta-analysis of 74 trials also revealed that drop-out rates were influenced by age, gender, duration of illness, duration of treatment and treatment setting.

Studies that have evaluated the efficacy of psychosocial interventions for comorbid substance misuse disorders have often based their results on the final sample of participants who completed the intervention. These results rarely account for the initial sample approached nor for dropout rates during the study. As a result, high drop-out rates can lessen the statistical power and the generalizability of those studies, and therefore reduce the possibility of detecting significant effects. If calculations of treatment outcomes and success rates are solely based on the small proportion of participants who complete the study, the results could only reflect the outcomes of those who have better prognostic factors and might not be representative of the population of individuals with comorbid severe mental disorder and substance misuse. It is therefore possible that the success rates reported do not represent the treatment reality of individuals with comorbid severe mental illness and substance misuse, given that those with worse prognostic factors will have likely dropped out of the treatment or study.

Recently, Hunt et al. (4) conducted a meta-analysis on the efficacy of existing interventions and programs for comorbid presentation of severe mental disorders and substance misuse. They covered many psychosocial interventions and programs and included 41 trials for a total of 4,024 participants. In sum,

the review reported a lack of quality evidence to support any one psychosocial treatment/program over standard care, and they encountered methodological difficulties, which hindered pooling and the interpretation of results. The meta-analysis did not, however, measure drop-out rates, preferring to exclude studies when these rates were too high.

The objective for the present review is to determine the drop-out rates in studies on psychosocial interventions for people with comorbid severe mental disorders and substance misuse (4), for both the experimental and control conditions. As a secondary objective, we will examine the influence of population (e.g., age, gender, diagnosis and substances used) and trial characteristics (e.g., duration of treatment, type of intervention) on drop-out rates.

METHODS

Eligibility Criteria

This meta-analysis included all RCTs with or without blind randomization which included a comparison between psychosocial intervention aiming at substance abuse reduction and a standard treatment in people with serious mental illness. Quasi-randomized studies were excluded. We opted for RCTs, considering that randomization was our minimal quality criterion, and that our previous meta-analysis on drop-out rates included only RCTs (25). Studies with missing data were excluded. We included participants diagnosed with both a diagnosis of substance misuse and severe mental illness, focusing primarily on psychotic spectrum disorders. Studies that included a vast spectrum of disorders were included only if the majority (e.g., $\geq$50%) of participants had a diagnosis of severe mental illness. We only included studies published in English or French.

Data Collection and Literature Search

We searched Prospero and the existing literature and no meta-analysis on drop-out rates during psychosocial intervention in dual-diagnosis was found. The current meta-analysis included all the articles from Hunt et al. (4) as well as new articles published since. In their Crochrane review, Hunt et al. (4) proceeded to search electronic databases using (*{PSY}* in Intervention) AND (*Substance Use* in Healthcare Condition) of STUDY in a study-based register that is compiled by systematic searches of majors resources (AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their updates. They also searched other resources, such as references lists, journal databases, trials registries, and personal contact. They then proceeded to select the studies by inspecting all citations and identified relevant abstracts, articles, and trials using their inclusion criteria, which have been inspected furthermore to ensure reliability (4). On the 41 articles retained by these authors, 33 were retained in the present article. Of the 8 excluded, 3 were not RCTs, 1 was excluded because of language barrier and 4 were duplicates. Because drop-out rates are the main focus of the present research, we also considered the articles rejected by this Cochrane review and proceeded to recuperate 10 articles that were excluded for high attrition rates by Hunt et al. (4). Two of these 10 articles were excluded because they were not RCTs. We also searched Psychinfo, Embase and PubMed databases using PRISMA criteria for new articles published between 2018 and 2021 using: "Psychotic*" OR "psychos*" OR "schiz*" OR "Severe mental illness" AND "substance use" OR "substance abuse" OR "substance misuse" OR "drug use" OR "Drug abuse" OR "Drug usage" OR "Substance related disorder*" OR "drug addiction" AND "Treatment" OR "intervention" OR "psychosocial" OR "program." We found 454 articles, and 4 new articles were retained based on title, abstract and full-text reads. In sum, we retained a total of 44 articles for analysis. Five other articles have been excluded during data extraction due to missing data. The Flow chart of the selection of studies is shown in **Figure 1**. Interventions were divided into four categories: Intervention (including CBT, Skills training, MI and CM), Specialized Integrated Services (Integrated treatments for dual disorders), Integrated services with outreach (e.g., assertive community treatment) and Support interventions (e.g., AA). The characteristics of the studies included in the meta-analysis are described in **Table 1**.

Data Extraction and Quantitative Data Synthesis

For drop-out rates, the number of participants suffering from a severe psychiatric disorder prior to treatment and at the end of treatment, respectively, was extracted from each study. Data on age (average age in terms of years), sex ratio (percentage of males and females), duration of treatment (number of weeks), treatment modality (interventions such MI and/or CBT, specialized integrated services, intervention with outreach, and support intervention), and percentage of patients with alcohol, cannabis and stimulant use disorders were also gathered. Data extraction was verified by two authors of this article. The *Comprehensive Meta-Analysis*-2 software (71) was used to conduct analyses of effect size, which corresponds to the drop-out rate (e.g., event rate), which represents the loss of participants prior or during treatment among those who agreed to undergo the treatment. Heterogeneity among effect size estimates was assessed with the Q statistics (72), with magnitude of heterogeneity being evaluated with the I^2 index (73). As the database was characterized by high heterogeneity (see below), we aggregated event rates across studies using random-effects models, which are more conservative than fixed-effect models, and seem to better address heterogeneity between studies and study populations (74). The possibility of publication bias was examined with Egger's test and visual inspection of funnel plot (75). Sub-analyses were conducted on treatment modality (e.g., intervention, specialized integrated services, integrated services with outreach and support interventions). Meta-regression analyses were used to examine the effects on drop-out rates of continuous variables, namely age, sex ratio, percentage of psychotic patients, duration of treatment, study quality and percentage of specific SUDs (e.g., alcohol, cannabis and stimulants). Finally, using event rates as the effect size, we calculated consent rates, which represent the number of patients

TABLE 1 | Details of included studies.

	Sample characteristics								Intervention details			Study details
	Mean age (interventions)	Mean age (controls)	% males	% psychotic spectrum	% cannabis	% stimulants	% Alcohol	N baseline	Intervention category*	Duration	Comparator	Study quality (/6)
Baker et al. (27)	31.71	30.05	75	37	46.80	22.80	60.80	160	Int.	One session (30–45 min)	TAU	4
Baker et al. (28)	28.83	28.83	78.20	86.60	73.10	42	67.30	130	Int.	10 sessions (1 per week)	Routine treatment	4
Barrowclough et al. (29)	31.1	31.1	92	100	61.11	66.67	61.11	36	Integrated	Over 9 months	TAU	4
Barrowclough et al. (30)	37.4	38.3	86.54	100	25.08	NS	47	327	Integrated	Up to 26 sessions over 12 months	TAU	6
Bellack et al. (31)	43.8	41.6	66.40	39.50	1.64	72.10	21.30	175	Integrated	2 times a week over 6 months	Standard care	4
Bogenschutz et al. (32)	42.74	41.09	52.13	18.20	NS	NS	100	121	Support Int.	12 weeks	TAU	2
Bond et al. (33)	31.5	31.5	79	70	NS	NS	61	97	With outreach	18 months	TAU	0
Bonsack et al. (34)	25	25.5	87.10	100	83.70	NS	NS	62	Int.	4–6 sessions over 6 months	TAU	2
Burnam et al. (35)	37	37	84	45	NS	NS	73.46	276	Integrated	3 months	Controls	2
Cather et al. (36)	23.2	23.1	72.50	100	11.20	NS	7.20	404	Integrated	2 years	Usual care	6
Chandler and Spicer (37)	43	43	71.98	54.30	11.70	30.10	31.10	182	Integrated	2.5 years	TAU	2
Drake et al. (38)	32.2	32.2	76.20	100	48.10	14	83	130	With outreach	3 years	TAU	4
Eack et al. (39)	39.68	34.67	71	100	73	NS	81.80	28	Int.	18 months	TAU	4
Edwards et al. (40)	20.9	21.3	72.30	100	48.90	NS	2.20	47	Integrated	3 months weekly sessions	Psychoeducation	4
Essock et al. (41)	36.4	36.6	72	76	NS	NS	73	198	With outreach	3 years	Standard care	2
Gaughran et al. (42)	43.76	44.65	57.64	100	NS	NS	NS	406	Integrated	9 months		6
Gouzoulis-Mayfrank et al. (43)	31.14	30.8	84	100	72	12	12	100	Integrated	18 months	TAU	2

(Continued)

TABLE 1 | Continued

	Sample characteristics								Intervention details			Study details
	Mean age (interventions)	Mean age (controls)	% males	% psychotic spectrum	% cannabis	% stimulants	% Alcohol	N baseline	Intervention category	Duration	Comparator	Study quality (/6)
Graeber et al. (44)	42.87	45	96.67	100	86	71	100	30	Int.	One session per week over 3–4 weeks	Educational treatment	2
Graham et al. (45)	39.5	37.69	84.75	71.19	46.70	3.30	40	59	Int.	4 to 7 sessions over 2 weeks	TAU	6
Hellerstein et al. (46)	31.9	31.9	76.60	100	76.60	87.20	91.50	47	Integrated	2 session per week over 8 monts	Non-integrated treatment	2
Herman et al. (47)	33.2	33.2	73.90	28.10	22.70	60.20	73.40	485	Integrated	18 months	standard treatment	2
Hjorthoj et al. (48)	26.6	27.1	75.73	82.52	100	NS	NS	103	Int.	1–2 sessions per week for the first month. and then one weekly over 6 months	TAU	6
Jerrell et al. (49)	NS	NS	NS	NS	NS	NS	NS	98	Integrated	12 months	Standard care	2
Johnson et al. (50)	24	25	86.75	88.36	72	NS	77	551	Int.	12 weeks	TAU	4
Kavanagh et al. (51)	22.6	22.6	60	100	76	24	88	25	Int.	6–9 sessions within 7–10 days.	Standard care	4
Kemp et al. (52)	20.6	20.8	81.25	100	NS	NS	NS	19	Int.	4–6 sessions	TAU	2
Kikkert et al. (53)	45.9	45.9	80.40	81.80	NS	NS	NS	154	Integrated	12 months	TAU	2
Lehman et al. (54)	31	30	74.07	68.52	50	35	79	54	Integrated	12 months	usual community mental health center (CMHC) and psychosocial rehabilitation service	2
Madigan et al. (55)	27.6	28.2	78.41	77.27	100	NS	NS	88	Int.	Once per week for 12 weeks (3 months)	TAU	4

(Continued)

TABLE 1 | Continued

	Sample characteristics								Intervention details			Study details
	Mean age (interventions)	**Mean age (controls)**	**% males**	**% psychotic spectrum**	**% cannabis**	**% stimulants**	**% Alcohol**	**N baseline**	**Intervention category**	**Duration**	**Comparator**	**Study quality (/6)**
Mangrum et al. (56)	36.5	36.6	49.07	20.93	NS	NS	NS	216	Integrated	12 months	TAU	0
Martino et al. (57)	35.35	35.35	65	51	35	64	82	23	Int.	One session	standard preadmission interview	2
Martino et al. (58)	29.71	34.1	72.70	100	45.80	70.80	41.70	44	Integrated	Two sessions	two-session standard psychiatric interview	2
McDonell et al. (59)	43.01	42.45	65.34	39.20	NS	96	47	176	Int.	3 months	TAU	2
McDonell et al. (60)	44.55	46.23	63.29	30.38	NS	NS	100	79	Int.	12 weeks	Noncontingent control group (reinforcers regardless of EtG results and treatment attendance)	2
Morse et al. (61)	40	40	80	80	19	NS	82	149	With outreach	24 months	Standard care	2
Mowbray et al. (62)	33.4	33.4	74	28	NS	21.67	NS	467	Integrated	Minimum 28 day stay in the ward	standard inpatient psychiatric treatment	2
Naeem et al. (63)	40.47	40.47	77.01	100	NS	NS	NS	105	Int.	6 sessions over 3 months	Standard care	4
Nagel et al. (64)	33.4 & 32.2	33	57	49	65	NS	63	49	Int.	From 2 to 6 months	Standard care	2
O'Connell et al. (65)	37.7 & 36.8	30.1	66	100	NS	NS	NS	137	Int.	3 months	Standard care	2
Petry et al. (66)	41.7	41.7	58	16	15.80	100	36.80	19	Int.	8 weeks	TAU	2
Rosenblum et al. (67)	42	44	68	30	NS	NS	NS	349	Support Int.	3–6 months	Waiting list control group	2
Swanson et al. (68)	32.85	34.87	63.63	44.63	NS	NS	NS	93	Int.	15 minutes of feedback and a 1 h session	Standard care	2

(Continued)

TABLE 1 | Continued

	Sample characteristics							Intervention details			Study details
	Mean age (interventions)	Mean age (controls)	% males	% psychotic spectrum	% cannabis	% stimulants	% Alcohol	N baseline	Intervention category	Duration	Comparator	Study quality (/6)
Tracy et al. (69)	NS	NS	50	NS	NS	NS	NS	30	Int.	4 weeks	Assessment only	2
Xie et al. (70)	32.4	32.4	77.60	100	45	15.20	82.70	223	Integrated	3 years		4

TAU, treatment as usual; Int., Intervention (e.g. CBT, contingency management, motivational interviewing). Integrated: Specialized integrated services; With outreach, integrated community treatment with outreach (e.g. assertive community treatment); Support Int, support interventions (e.g., 12–steps).

who consented to participate in the study relative to those who were approached by the research team.

Data Analysis

Hunt et al. (4) appraised study quality, and evidence was rated as low or very low quality. They report a high or unclear risk of bias because of poor or inadequately reported trial methods, imprecision due to sample sizes, low event rates and wide confidence intervals. We also assessed study quality for the RTCs that were retained for the present article, using Jadad criteria (76). Random allocation, allocation concealment and blindness were the three criteria used, and we adapted the scale for the present research by excluding poor ratings for withdrawals and drop-outs because it was what interested us for the present study. To ensure validity, we conducted two quality evaluation by two researchers to validate and verify Jadad scores. Studies were of low to moderate quality, primarily because of missing data and absence of allocation concealment. Blindness was also not reported or described in a large proportion of the studies included. Study quality for each trial, as determined using Jadad criteria, is detailed in **Table 1**.

RESULTS

Drop-Out Rates

In the 42 treatment arms, the composite drop-out rate was 27.2% (CI, 95%: 21.0–34.3%) (**Table 2**). In the case of treatment-as-usual (TAU), the aggregation of 32 studies produced a composite drop-out rate of 20.5% (CI, 95%: 14.2–28.6%) (**Table 2**). As illustrated in **Figure 2**, a publication bias was present (Kendall's Tau $= -0.309$; $p = 0.004$; Egger's test: $t = 3.197$; $p = 0.003$). For both experimental treatment and TAU, results across treatment arms were characterized by very high levels of heterogeneity ($I^2 = 90\%$ and 90.1%, respectively) (**Table 2**).

Secondary Analyses

A sub-analysis on treatment modality showed that drop-out rates were fairly similar across interventions (28.7%; 20 treatment arms), specialized integrated services (27.3%; 16 treatment arms) and support therapies (28.3%; 2 treatment arms), but that drop-out rates were lower in trials on interventions with outreach (11.1%; 4 treatment arms) (**Table 2**). Within each treatment modality, results were characterized by high levels of heterogeneity (between 76 and 96.7%).

Meta-regression analyses on the experimental treatment arms showed a positive association between stimulant use disorder (StUD) and drop-out rates [16 experimental treatment arms; slope (β) $= 0.014$; $p = 0.0001$] (**Table 3; Figure 3**). That is, the highest drop-out rates were observed in trials including the highest proportion of patients with as StUD. Conversely, age ($p = 0.530$), sex ratio ($p = 0.561$), percentage of psychotic patients ($p = 0.119$), duration of treatment ($p = 0.129$), study quality ($p = 0.967$), percentage of patients with alcohol use disorder ($p = 0.464$) and percentage of patients with cannabis use disorder ($p = 0.091$) had

TABLE 2 | Primary and secondary analyses: drop-out rates across interventions.

Analysis	Number of treatment arms	Rate (%)	*p*-value	Confidence interval	Heterogeneity
Main analysis					
Experimental treatment	42	27.2	0.0001	(21.0–34.3)	$Q = 409.3$; $p = 0.0001$; $I^2 = 90\%$
TAU	32	20.5	0.0001	(14.2–28.6)	$Q = 312.5$; $p = 0.0001$; $I^2 = 90.1\%$
Sub-analyses (for experimental treatment arms only)					
Intervention *	20	28.7	0.0001	(19.5–40.2)	$Q = 79.2$; $p = 0.0001$; $I^2 = 76\%$
Specialized Integrated Service	16	27.3	0.001	(17.3–40.3)	$Q = 269.7$; $p = 0.0001$; $I^2 = 94.4\%$
Outreach	4	11.1	0.002	(3.3–31.5)	$Q = 14.5$; $p = 0.002$; $I^2 = 79.4\%$
Support therapy	2	28.3	0.209	(8.4–62.8)	$Q = 30.6$; $p = 0.0001$; $I^2 = 96.7\%$

*TAU, treatment-as-usual; *Intervention, motivational interviewing and/or cognitive behavioral therapy.*

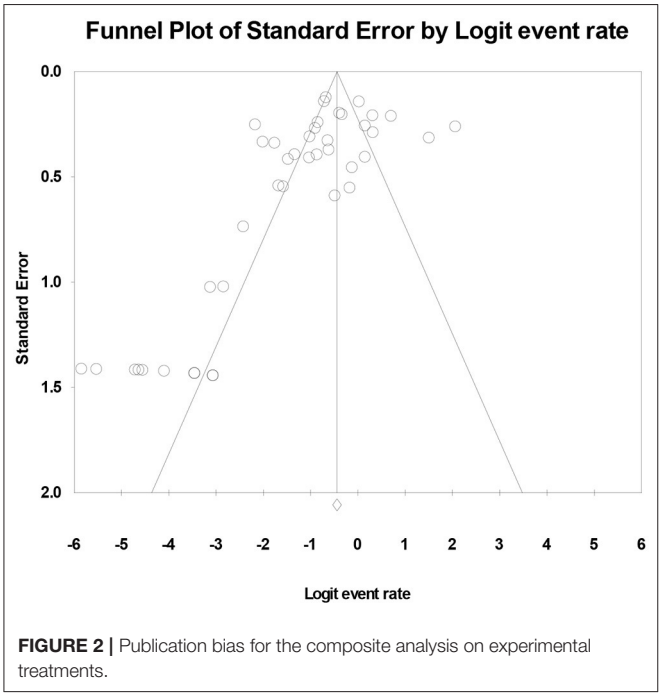

FIGURE 2 | Publication bias for the composite analysis on experimental treatments.

TABLE 3 | Predictors of drop-out rates for experimental treatments.

Predictor	Number of experimental treatment arms	Slope
Age	39	$\beta = 0.021$; $p = 0.530$
Sex ratio	41	$\beta = 0.012$; $p = 0.561$
Duration of treatment (in weeks)	40	$\beta = -0.010$; $p = 0.129$
% of patients with psychosis	40	$\beta = -0.013$; $p = 0.119$
% of patients with alcohol use disorder	30	$\beta = 0.008$; $p = 0.464$
% of patients with cannabis use disorder	27	$\beta = 0.015$; $p = 0.091$
% of patients with stimulant use disorder	16	$\beta = 0.014$; $p = 0.0001$
Study quality	42	$\beta = -0.006$; $p = 0.967$

no significant influence on drop-out rates across trials (**Table 3**).

Consent Rates

In the 29 studies offering this information, we found that the composite consent rate was 44.4% (CI, 95%: 0.365–0.526; $p = 0.178$). Across studies, results were highly heterogeneous ($Q = 2{,}088.2$; $p = 0.0001$; $I^2 = 98.7\%$).

DISCUSSION

The objectives of the present research were to determine dropout rates in studies on psychosocial interventions for people with a dual diagnosis of severe mental illness and substance abuse. We also wanted to examine the influence of population (e.g., age, gender, diagnosis and substances used) and trial characteristics (e.g., duration of treatment, type of intervention) on drop-out rates.

The dropout rate of 27.2% for the experimental arm and of 20.5% for TAU suggest that, on average, close to one third of participants in treatment studies never complete the treatment. Furthermore, the publication bias found suggest that studies under report their drop-out rates, which brings us to suppose that the actual drop-out rates might be even higher. Dropout rates results had high heterogeneity (I^2 ranging from 76 to 96,7%). This variability might be explained by publication bias, high differences in outcomes measured in studies, and differing ways in which psychosocial interventions were delivered.

Villeneuve et al. (25) found a dropout rate of 13% in their meta-analysis on dropout from psychosocial treatment among individuals with schizophrenia spectrum disorder, which is less than half of what we found in our experimental arm. One of the major differences between their study and ours is that we included persons with both schizophrenia spectrum disorder

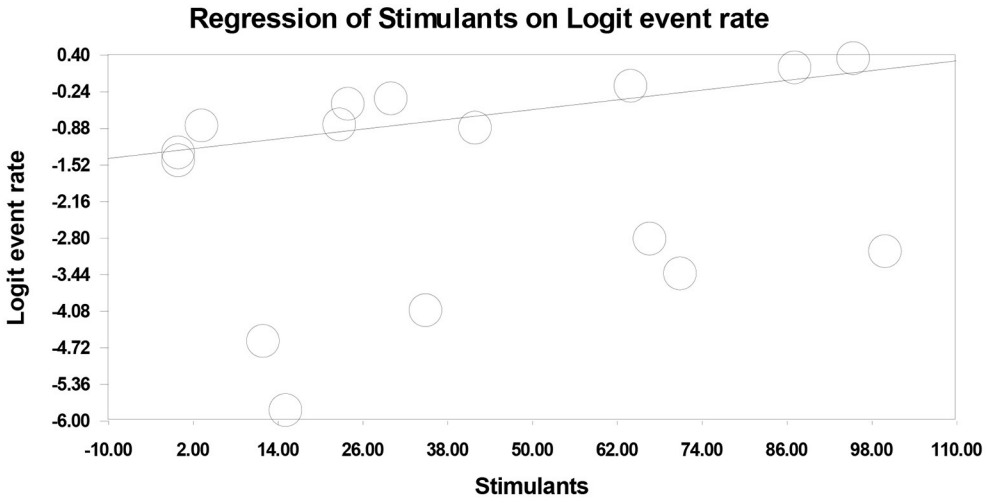

FIGURE 3 | The influence of percentage of patients with stimulant use disorder on drop-out rates across experimental treatments.

and substance use disorder. Differences in dropout rates could partly be explained by stimulants use, since the dropout rates appeared worse in those with stimulant use. This difference in results could also possibly be explained by higher severity of symptoms, impulsivity, and lower motivation in our clinical population, although these were not specifically analyzed here. Individuals with a dual diagnosis of psychotic spectrum disorder and substance use disorder in general present with higher symptom severity and more relapses, as well as more deficits in executive functions like planning and thinking before acting, more impulsivity and less motivation in general (77, 78). Another factor that could explain the drop-out rates result is a poor therapeutic alliance (23, 24), and demanding requirements for certain interventions (for example, many interventions required participants to come to clinics regularly, in person) even though motivation is often an issue with this population.

Research on dual diagnoses focus on developing and replicating studies on specialized treatments to demonstrate their efficacity. However, these different interventions and treatment programs present few similarities and vary greatly on the type of interventions they include, the objectives, and the symptoms targeted (79). This brings us to wonder if the research focus should shift away from a focus on the efficacy of specialized treatments, since there is a high dropout rate form experimental treatments and, therefore, the results might only represent the small portion that accept to participate and complete the treatment (25).

Our results also showed a lower drop-out rate, of 11,1%, for intensive programs like assertive community treatments. Although this rate was based on the aggregation of only 4 trials, it is noteworthy that this rate was half of the rate found in more specific treatments in this review. Such programs focus on engaging the participant, are long-term, and do not specifically aim on obtaining results regarding substance misuse (80, 81). In their meta-analysis, Hunt et al. (4) found no difference between treatments in terms of improved outcomes in terms of lost to treatment, death, alcohol or substance used, global functioning and general satisfaction, suggesting that intensive treatment programs like assertive community treatments did not fare better or worse than the other treatments or services analyzed. Most studies search for gains in terms of outcomes (decreased substance use, improved symptoms and global functioning for example), yet, with complex clinical populations such as people with comorbid substance misuse and psychotic disorders, the evolution in terms of clinical outcomes can be slow, suggesting a need for long-term treatments that focus on engaging the person and developing a strong therapeutic alliance. It is also important to consider the complexity of this clinical population. There is often history of abuse and trauma (82, 83), emotional self-regulation issues (84), frequent comorbidity with personality disorders (85), and with anxiety disorders (86), and important cognitive and functional deficits. There is also medication to consider, which can lead to a multitude of side effects depending on dose and type of medication, that can interact with substance misuse. These issues can be a challenge to work with since there are many parameters to account for, and can make it difficult to develop a strong and good therapeutic alliance both from the client and the clinician's perspective (87–89). Interventions should perhaps focus more on engaging participants by developing a strong therapeutic alliance, with the hope of eventually motivating them in working on their substance misuse problem. As discussed, many reasons for dropout reported by participants in studies were related to engagement with the therapist or team (23, 24). This suggests that a more engaging approach to treatment, with outreach such as in assertive community treatment teams, might be more successful in the long run in keeping clients into treatment. Having intensive treatment teams trained to work with psychotic spectrum and substance use disorders (and more specifically in stimulant use disorders) while targeting the development of a

good alliance with the participant appears promising to prevent dropout rates.

Although we did not find a significant association between study quality and drop-out rates, it must be pointed that studies included in the current meta-analysis were in vast majority of low to moderate quality. This was mostly due to the absence of allocation concealment most trials and due to the fact that blindness was also not reported or described in most cases. At face value, this may seem to be a limitation, as there were few high quality to analyze. However, one may argue that the access to low / moderate quality trials may be better suited for the assessment of drop-out rates. This can be explained by the fact that higher quality studies often have more resources at their disposition to conduct their research, and thus are more able to invest in research teams and labs that can either follow the participants more closely or pay them more for their participation. Thus, higher the quality trials may, in theory, be more biased in the assessment of dropouts. On the other hand, low quality studies might in fact be more accurate in assessing the clinical reality of offering interventions to people with a severe mental illness and concurrent substance abuse. As such, having more low-quality studies in the context of this research topic is advised as these are perhaps more ecologically valid than high quality studies. In the future, it will be important to collect, in a systematic manner, data on drop-out rates during psychosocial interventions delivered in non-randomized trials. Although, as described by Hunt et al. (4), treatment outcomes are not impressive with this population, future studies should also investigate how drop-out rates affect actual treatment effect sizes.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

MB conducted the review and wrote the article. TL co-supervised MB, edited the article. BC conducted the interrater agreements. JH-R formatted the article, references and helped with the data search, and SP co-supervised MB and conducted the analyses. All authors contributed to the article and approved the submitted version.

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