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Timing of Cannabis Exposure Relative to Prodrome and Psychosis Onset in a Community-Based First Episode Psychosis Sample

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Abstract

Cannabis has been implicated as both a potential cause and adverse prognostic factor in psychotic disorders. Investigating the contributory role of cannabis toward the overall burden of psychotic illnesses may represent an important step toward psychosis prevention and treatment. The current study samples consecutive admissions (N = 246) to two community based first-episode psychosis services to characterize timing of cannabis use relative to psychosis and attenuated symptom onset, differences between those with and without cannabis exposure, and the association of age at first cannabis exposure with clinical and demographic variables. Both cannabis exposure (78%) and cannabis use disorders (47%) were highly prevalent at admission. In 94% of participants, cannabis use preceded the onset of both attenuated and full-threshold psychosis symptoms by several years. Earlier age at first exposure to cannabis was associated with younger age at prodrome and psychosis onset, worse premorbid functioning, and greater severity of cannabis use disorder at admission. The timing of first exposure to cannabis may have individual prognostic as well as public health significance. Documenting the prevalence and impact of cannabis use in early psychosis samples, as well as the overall incidence of psychotic disorders, will be of vital public health significance as the United States enacts cannabis legalization and cannabis products become more widely available.

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Dr. Kline conducted the analyses, drafted the manuscript, and prepared the manuscript for publication. Dr. Ferrara, Mr. Li, and Dr. D'Souza contributed content expertise and assisted with manuscript preparation. Drs. Keshavan and Srihari designed the study and supervised all aspects of data collection and analysis. All authors have contributed to and reviewed this manuscript.

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Keywords

cannabis; marijuana; first episode psychosis; prodrome; schizophrenia

1. Introduction

Cannabis use is common and consequential in the early phases of schizophrenia. A history of cannabis use among adolescents and young adults receiving treatment for a first episode of psychosis is common, both in the immediate circumstances leading to the onset of psychosis as well as more habitually throughout adolescence (Myles et al., 2016). Ongoing cannabis use in the context of first episode psychosis (FEP) is also common (Marino et al., 2020). Cannabis use in patients with diagnosed illness can exacerbate symptoms and serves as a very strong predictor of relapse and/or chronicity of illness (Patel et al., 2016; Schoeler et al., 2016a; Schoeler et al., 2016b; Seddon et al., 2016).

Cannabis, specifically the delta-9-tetrahydrocannabinol (THC) constituent, has been implicated as a cause of transient psychotic symptoms and a risk factor for schizophrenia (Radhakrishnan et al., 2014; Patel et al., 2020). Recent research has highlighted cannabis use prevalence and THC content as important population-level risk factors for chronic psychosis (Di Forti et al., 2019). However, the absolute risk of psychotic disorders for cannabis users remains small, and many individuals with psychosis have no history of cannabis use. Cannabis use is neither necessary nor sufficient for psychosis development; rather, the cannabis “route” can be conceptualized as one among several possible pathways to psychosis within a diathesis-stress framework (Loberg et al., 2014; Wilkinson et al., 2014).

The role of cannabis use in the worsening of prodromal symptoms preceding FEP onset remains unclear. Studying cannabis use among individuals at “clinical high risk” (CHR; that is, expressing sub-threshold symptoms representing a prodromal stage of psychosis) has yielded limited insights. In a meta-analysis of prospectively followed individuals at CHR for psychosis, cannabis use did not significantly predict conversion to a psychotic disorder (Oliver et al., 2020). Critiques of the CHR paradigm, however, have pointed out that the low and/or uneven progression to psychotic disorders within this population limits useful inferences about the relationship between cannabis and schizophrenia from CHR samples (Ajnakina et al., 2018; Malhi et al., 2021). So, although cannabis appears to pose risks to both the general population and individuals experiencing psychosis, the impact of cannabis on the initiation and worsening of subthreshold psychosis symptoms for those who do progress to schizophrenia remains obscure.

Over the past decade, the United States has enacted policies of cannabis liberalization, with full legal access to cannabis for adult non-medical (“recreational”) users in some states (Pacula & Smart, 2019). At the same time, use among young adults has become more prevalent (Odani et al., 2019), and cannabis products have increased in potency (ElSohly et al., 2016). Taken together, these trends could result in higher incidence of FEP onset, thereby placing greater demands on clinical services. In summary, there is an urgent need to better understand the prevalence, impact, and timing of cannabis use in early phase clinical samples. Few such studies have been conducted in the United States (Marino et al., 2020).

The growth of specialty team-based coordinated specialty care (CSC) services for FEP across the United States (Dixon et al., 2018) provides an opportunity to better understand the role of cannabis in early course schizophrenia spectrum disorders. The current study utilized an ecologically relevant U.S. community-based sample of patients admitted to two CSC services between 2014–2019. Specific aims are to characterize the timing of cannabis exposure relative to the attenuated positive syndrome and psychosis onset, and to evaluate demographic and clinical differences between those with and without cannabis exposure.

2. Methods

2.1. Setting and sampling

Subjects were recruited from consecutive admissions to CSCs based in two public community mental health centers in the Northeastern United States: the clinic for Specialized Treatment Early in Psychosis (STEP) at the Connecticut Mental Health Center in New Haven (Srihari et al., 2009) and the clinic for Prevention and Recovery in Early Psychosis (PREP®) at the Massachusetts Mental Health Center in Boston (Caplan et al., 2013). The neighborhoods surrounding both the STEP and PREP clinics are densely populated, racially diverse urban and suburban areas with significant immigrant populations. As part of a two-site study of early detection, both CSCs used the same broad and simple eligibility criteria to inclusively engage individuals between 16–35 years, with a putative primary non-affective psychotic disorder of onset within the prior three years. Exclusions were made for psychosis established as secondary to a medical condition, primary affective disorder or substance-induced psychotic disorder (including cannabis). Antipsychotic exposure of any duration was not an exclusion or inclusion criteria, though patients who had already received CSC treatment at another clinic were excluded. An early detection campaign targeted STEP's catchment for four years, after an initial year of usual detection, while PREP continued to offer usual detection throughout. The current analysis includes subjects enrolled across the entire study period (February 1st 2014 to January 31st 2019). A detailed protocol has been published (Srihari et al., 2014).

All study procedures were approved and monitored by the Institutional Review Boards of Yale University, Beth Israel Deaconess Medical Center, and Massachusetts Department of Mental Health. Patients provided informed consent to participate in this study.

2.2 Measures

2.2.1 Baseline characteristics—Age, race, ethnicity, educational attainment of patients and their parents, type of health insurance (an indication of socioeconomic status in the United States; recorded as public or none vs. private) and country of origin was recorded at clinic enrollment at each site.

2.2.2 Premorbid functioning—Interviewers administered the Premorbid Adjustment Scale (Cannon-Spoor et al., 1982) and the Wide Range Achievement Test Word Reading Task (Wilkinson & Robertson, 2006)

2.2.3 Cannabis use—Participants were asked, “have you ever used cannabis/marijuana?” and “at what age did you first try cannabis/marijuana?” Answers were recorded as expressed. Raters also completed the “Drug Use Scale” (DUS), an interview-rated 5-point scale based on DSM criteria for severity of substance use disorder over the prior six months: 1 = abstinence, 2 = use without impairment, 3 = abuse, 4 = dependence, and 5 = dependence with institutionalization (Drake et al., 1990).

2.2.4 Diagnosis, age of prodrome and psychosis onset, and duration of untreated psychosis—Primary and substance use related diagnoses were determined via Structured Clinical Interview for the DSM-IV (SCID-IV; First et al., 2002). Criteria established within the scale for Structured Interview of Psychosis-Risk Syndromes (SIPS; McGlashan et al., 2010; Yovienne Sykes et al., 2019) were used to differentiate psychosis from the prodrome or Attenuated Psychosis Syndrome (APS), and to date the onset of each illness phase (Ferrara et al., 2021). Collateral information was obtained for nearly all participants from parents or other family members as well as review of medical records. Based on available literature, we expected variability in ascertainment of information about the prodrome: e.g., that some participants would not be able to confirm this phase, or that others might report attenuated symptoms but without a defined onset (Schultze-Lutter et al., 2015; Shah et al., 2017). Therefore, each participant was classified into one of four mutually exclusive categories: (i) Very acute onset psychosis (no prodrome); (ii) Prodrome identified with estimate of APS syndrome onset date; (iii) Prodrome identified but unable to estimate APS syndrome onset date; and (iv) Unable to determine presence or absence of APS.

Interviewers wrote a narrative describing each participant’s current symptoms, psychiatric history, APS categorization, dates of treatment initiation, and the interviewer’s determination as to dates of onset of APS and full psychosis. Narratives were presented on weekly calls with at least one lead investigator from each site present to ensure consensus regarding diagnosis, APS and psychosis onset dates, and DUP. Age at APS and psychosis onset was calculated for each participant using birthdate and consensus dates of APS/psychosis onset. Duration of Untreated Psychosis (DUP) was calculated as the elapsed time between psychosis onset and CSC admission.

2.2.5 Clinical status and functioning—Participants were assessed at enrollment with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS; Kay et al., 1987), the SIPS Global Assessment of Functioning (GAF; McGlashan et al., 2010), the Global Functioning Social and Role Scales (GF-S/GF-R; Piskulic et al., 2011), the Hopkins Verbal Learning Test (three-trial immediate recall only; Brandt & Benedict, 2001), the Symbol Coding task from the Brief Assessment of Cognition in Schizophrenia battery (Keefe et al., 2008), and the Managing Emotions subtest from the Myers-Salovey-Caruso Emotional Intelligence Test (Mayer et al., 2003). For these three neuro/social cognitive tests, age and gender normed t-scores were obtained using Matrics Consensus Cognitive Battery (Nuechterlein et al., 2008) scoring software. Interviewers participated in quarterly reliability training to ensure consistent scoring on clinician-rated assessments across sites.

2.3 Analyses

Independent samples t-tests and chi-square tests were conducted to examine differences between participants with and without cannabis exposure. For t-tests, the assumption of equal variances was tested via Levene's test; reported statistics represent adjusted values when the assumption was violated. Pearson correlations were used to identify associations between age of cannabis exposure, current severity of cannabis use, DUP, and clinical and cognitive illness severity. Participants with a missing data point were excluded per analysis but retained within the sample overall.

3. Results

Two hundred forty-six subjects were enrolled. The majority were male (71%) with a mean age of 22.27. The sample was broadly representative of the clinic catchments, with a significant proportion who identified as black (45%), Hispanic/Latino (19%), or first-generation immigrant (16%). Median DUP was 224 days (25–75 IQR = 67–533). Primary diagnoses were schizophrenia (59%), schizoaffective disorder (19%), schizophreniform disorder (8%), brief psychotic disorder (1%), and unspecified psychotic disorder (13%). With regard to prodromal illness, 11 participants (4%) had a very acute onset with no APS period, 204 (83%) had a discernible APS onset ranging from 1 day to 12 years before psychosis onset, 12 (5%) had confirmed attenuated symptoms without an estimable date of onset, and 19 (8%) could not be categorized. Additional sample descriptors are summarized in Table 1.

For those with SCID substance use disorder data (n = 245), a majority (133, 54%) had a current or lifetime substance use disorder (SUD). The vast majority of SUDs (115 or 47% of the sample) involved cannabis use disorder (CUD) alone or in combination with other substances (including nicotine). Among those with CUD, 85 (70%) met criteria for a current CUD while the remainder were in remission. DUS ratings for cannabis aligned well with SCID diagnoses: 146 (59%) of participants acknowledged using cannabis at least once in the past six months, and 85 (35%) met abuse or dependence criteria within the past six months. Total cannabis exposure was bimodally distributed, with 54 participants (22%) reporting no lifetime use and 121 (49%) reporting 300+ episodes of lifetime use. None of the individuals with known cannabis use history (for example, by medical record) denied having used the substance on interview.

Individuals with a history of cannabis use were more likely to be male (χ^2 [1, 246] = 17.05, $p < .001$) and to have been born in the United States (χ^2 [1, 246] = 9.08, $p = .003$), but were otherwise indistinguishable from non-users in terms of other variables, including demographic factors (race, ethnicity, mother's education, and insurance status), premorbid functioning, clinical presentation at admission to CSC, age of APS and psychosis onset, APS duration, and DUP (see Table 2).

Of the 192 individuals who acknowledged any exposure to cannabis, 191 (99.5%) were able to report age of first use. The average self-reported age of first cannabis use was 15.67 and normally distributed (range, 5–25). First cannabis use for the vast majority (94%) occurred prior to FEP onset, for 5% at the same time as FEP onset, and for only 1% after FEP onset.

Similarly, 80% reported first using cannabis prior to APS, 11% at the same time as APS onset, and 9% after APS onset. Figure 1 shows the distribution of age cannabis initiation, APS onset, and FEP onset.

Age at first use was normally distributed (range = 2–25) and significantly correlated with the general subscale of the premorbid adjustment scale (r=−.20, p=.005), current cannabis use severity (rated on the Drug Use Scale, r=−.16, p=.027), age at APS onset (r=.20, p=.014), and age at FEP onset (r=.20, p=.006). Age at first use was not significantly associated with other variables measured at admission (listed in Table 1).

4. Discussion

Cannabis use and abuse was highly prevalent in this sample of FEP patients served in these racially diverse, mostly urban United States settings. The vast majority (78%) of incoming FEP patients across these two programs acknowledged at least one prior episode of cannabis use, 59% had used cannabis in the past six months, and 47% met clinical criteria for a current or lifetime CUD. For context, in 2017 the prevalence of past-month cannabis use was estimated to be 22% of young adults ages 18–25 in the United States, and the prevalence of CUD in this age group was estimated at 5% (Bose et al., 2018). The elevated prevalence of cannabis use disorders in this sample may be a function of using the complete SCID, which includes the full range of severity of substance use disorders and may therefore have relatively few false negatives. That cannabis exacerbates psychosis symptoms for many users with FEP thus qualifies their use, by this definition, as disordered; however, study clinicians were able to differentiate between FEP participants with recent cannabis use (n = 146) and those with a current CUD (n = 85).

Nearly all cannabis users in the FEP sample reported that they began using cannabis prior to the onset of psychosis or psychotic-like symptoms. This is consistent with prior findings (Myles et al., 2016) and supports a growing consensus (Rey et al., 2004) that elevated cannabis use among those with psychosis and psychosis-risk syndromes is unlikely to be fully attributable to attempts to alleviate distress or confusion stemming from emerging psychosis. A small minority (9%) of patients did report that they began using cannabis after the onset of attenuated psychotic symptoms, for whom a self-medication role of cannabis is more plausible (Gill et al., 2015).

Within this sample, cannabis exposure was not associated with known socioeconomic determinants of health such as race, Hispanic/Latino ethnicity, mother’s educational attainment, or private insurance (a proxy for socioeconomic status in the United States). This finding is consistent with general population research showing that cannabis use among adolescents and young adults in the United States is less socioeconomically determined relative to other substances such as alcohol (Haberstick et al., 2014).

Earlier age of first cannabis use was significantly associated with worse premorbid functioning, more problematic use at time of admission, and earlier age at both prodrome and psychosis onset: all factors known to predict poorer prognosis (Alvarez-Jimenez et al., 2012; Goldberg et al., 2011; Schoeler et al., 2016b; Tuulio-Henriksson et al., 2004).

Other studies have found earlier age at illness onset for psychosis patients with a history of cannabis use vs. cannabis-naïve patients (Large et al., 2011). Our finding is slightly more nuanced and replicates the results obtained by DiForti and colleagues (2014), who showed that younger age at first cannabis use (rather than any history of use) predicts younger age at psychosis onset. Some have pointed out that the association of cannabis use with younger age of psychosis onset may be confounded by sex (Myles et al., 2012); however, in the current study, males were likelier to have ever used cannabis but did not differ from females regarding age at first use. These findings suggest that timing of first exposure to cannabis may be an important prognostic factor for individuals who go on to develop psychosis.

Strengths of this study include a well-defined early psychosis sample that is reflective of the kinds of patients targeted by United States CSCs, a rigorous consensus-based process for retrospective dating of APS and psychosis onset, and a long period of continuous enrollment. Few studies on the prevalence and impact of cannabis use prior to and during a first episode of psychosis have been conducted in the U.S. The timing of the study is also notable, as data collection took place immediately before full legalization of adult cannabis use in Massachusetts and much of the United States overall. The liberalization of cannabis laws in the United States constitutes a historic policy and culture change that may impact the incidence of psychosis as these policies take effect.

The primary weaknesses of the study are the reliance upon self-report data for cannabis exposure and ongoing use, as well as potential recall bias regarding age of first use and first psychotic symptoms. The exclusion of individuals with established “cannabis-induced psychotic disorder” from the FEP treatment sites at which the study was conducted may also represent a weakness, as there is emerging evidence that this diagnosis is often unstable and progressive toward chronic recurrent psychotic illness (Starzer et al., 2018). Additionally, it is important to note that several analyses, especially those involving dichotomous variables, may have been underpowered to detect significant effects.

Our findings suggest that delaying initiation of cannabis use among young adolescents may have substantial public health benefits, a conclusion shared by researchers and policy makers interested in a diverse array of social and psychiatric outcomes (Murray & Hall, 2020; Nguyen et al., 2020). This may involve policies such as prohibiting sales of cannabis preparations that are enticing to young consumers (e.g., edible cannabis candies) as well as public health interventions directed at general population settings such as schools or indicated settings such as general adolescent psychiatry clinics. The high prevalence of cannabis abuse noted within the FEP clinical population also suggests the need for specialty care sites to focus treatment more explicitly on cannabis reduction. Continuing to document the prevalence and impact of cannabis use in FEP samples, as well as the overall incidence of psychotic disorders, will be of vital public health significance as the United States enacts cannabis legalization and cannabis products become more widely available to American consumers.

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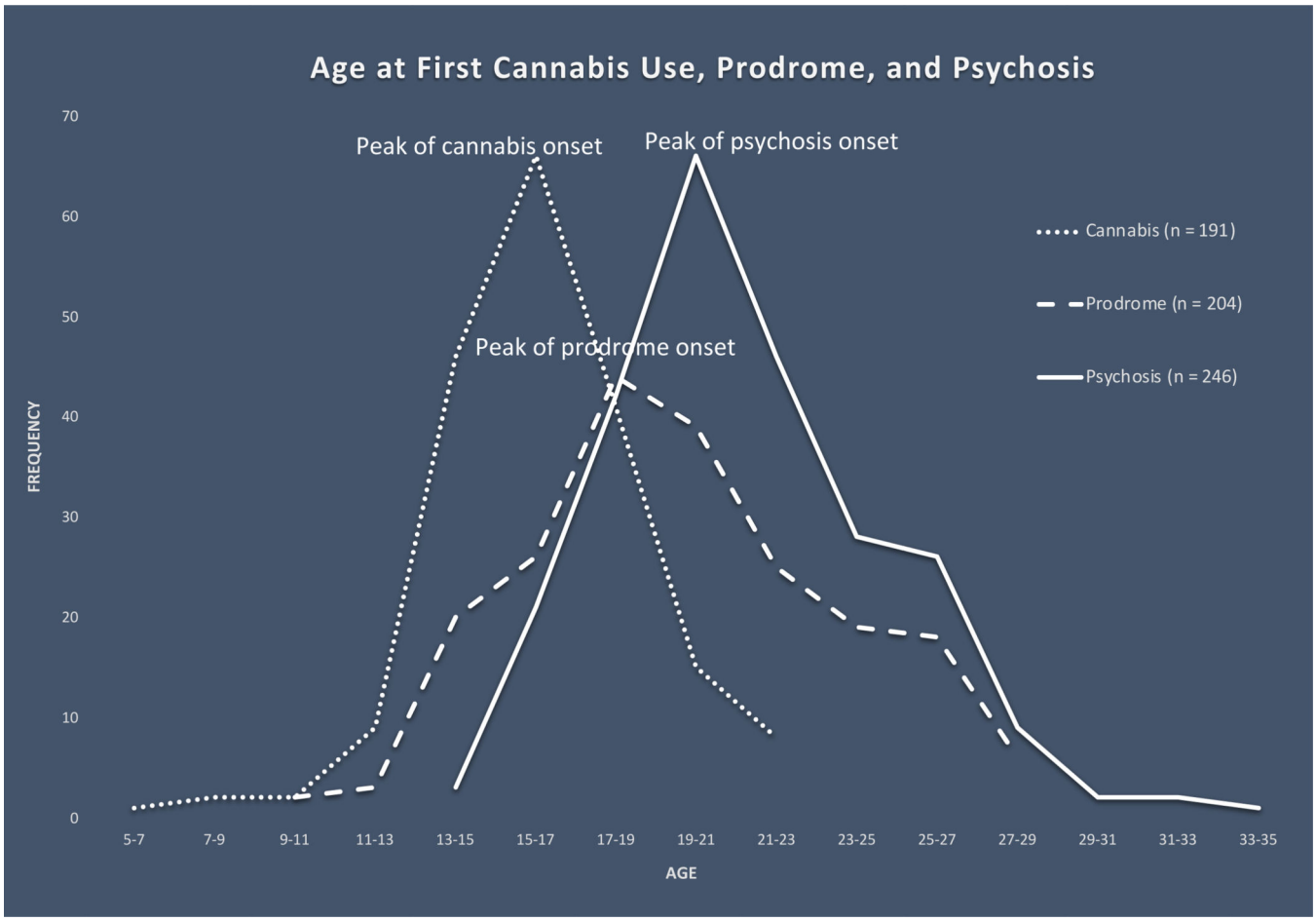

Figure 1.
Age at First Cannabis Use, Prodrome, and Psychosis

Table 1

Sample Demographic and Clinical Characteristics ($N = 246$)

	N (%)		Mean (SD)
Gender		Age at Study Enrollment	22.27 (3.53)
Male	174 (71%)	Age at APS Onset[1]	19.80 (4.04)
Female	72 (29%)	Age at Psychosis Onset	21.28 (3.56)
Race		Clinical and Functional Assessments	
Native North American	1 (<1%)	PANSS Pos. Total	18.83 (6.23)
Asian	7 (3%)	PANSS Neg. Total	17.61 (6.78)
Black	110 (45%)	PANSS Gen. Total	35.08 (9.16)
White	79 (32%)	GAF	33.55 (11.15)
Middle Eastern	1 (<1%)	GF-Role	3.95 (2.20)
Central/South American	7 (3%)	GF-Social	5.09 (1.48)
Multiple Races	37 (15%)	HVLT T-Score	35.91 (8.51)
Refused	4 (2%)	BACS-SC T-Score	31.76 (11.67)
		MSCEIT-ME T-Score	40.44 (12.36)
Latino/Hispanic Ethnicity	46 (19%)		
		Days to FEP treatment service (DUP)	344.37 (321.69)
Born in United States/Puerto Rico	206 (84%)	APS Duration (years)	1.53 (2.09)
Socioeconomic Status		Premorbid Functioning	
Mother Completed College	88 (36%)	PAS Childhood Total	5.35 (3.87)
Private Insurance	80 (33%)	PAS Adolescence Total	8.15 (4.97)
		PAS General Total	15.98 (7.51)
Prior Cannabis Exposure	192 (78%)		
		Educational Attainment	
		Years of Education	12.52 (1.92)
		WRAT Reading Standard Score	99.71 (16.30)
		Cannabis Use	
		DUS Cannabis Score	1.94 (1.04)
		Age at First Cannabis Use	15.67 (2.69)

[1]Time of onset of attenuated psychosis symptoms was determined for 204 participants via retrospective SIPS interview. Other participants reported no APS period preceding psychosis (n = 11) or a date of APS onset could not be estimated (n = 31).

APS = Attenuated Psychosis Syndrome

BACS-SC = Brief Assessment of Cognition in Schizophrenia Symbol Coding

DUS = Drug Use Scale

GAF = SIPS Global Assessment of Functioning Scale

GF = Global Functioning Scale

HVLT = Hopkins Verbal Leaning Test

MSCEIT-ME = Mayer-Salovey-Caruso Emotional Intelligence Test Managing Emotions Subscale

PANSS = Positive and Negative Syndrome Scale for Schizophrenia

PAS = Premorbid Adjustment Scale

WRAT = Wide Range Achievement Test

Table 2.

Clinical and demographic differences between patients with and without exposure to cannabis

	No Exposure (n = 54)	Cannabis Exposed (n = 192)	Comparison of Means		
	Mean (SD)	**Mean (SD)**	***t***	***P***	***Cohen's d***
Age at assessment[1]	21.80 (4.16)	22.41 (3.33)	−0.99	.324	−0.17
Years of education	12.32 (2.00)	12.57 (1.90)	−0.85	.398	−0.13
Age at APS onset	19.03 (4.26)	20.02 (3.96)	−1.46	.146	−0.25
Age at psychosis onset[1]	20.60 (4.22)	21.47 (3.33)	−1.40	.166	−0.25
Prodrome duration (years)	1.31 (1.81)	1.59 (2.17)	−0.76	.450	−0.13
DUP (days to FEP treatment)	415.06 (284.46)	324.49 (329.36)	1.84	.067	0.28
Current GAF	34.28 (11.75)	33.34 (11.00)	0.54	.588	0.08
GF-Role	4.06 (2.32)	3.92 (2.17)	0.41	.683	0.06
GF-Social	5.02 (1.46)	5.11 (1.49)	−0.42	.675	−0.07
PANSS positive symptoms	17.93 (5.86)	19.08 (6.32)	−1.20	.231	−0.19
PANSS negative symptoms	18.74 (6.72)	17.30 (6.77)	1.39	.167	0.21
PANSS general symptoms	35.09 (8.15)	35.07 (9.45)	0.01	.989	<0.01
Premorbid adjustment - childhood	5.38 (4.23)	5.35 (3.77)	0.05	.958	0.01
Premorbid adjustment - early adol.	9.02 (5.04)	7.91 (4.93)	1.44	.151	0.22
Premorbid adjustment - general[1]	15.73 (5.97)	16.05 (7.89)	−0.32	.750	−0.04
WRAT Reading standard score	101.27 (16.46)	99.28 (16.27)	0.78	.437	0.12
HVLT T-score	34.09 (8.27)	36.43 (8.52)	−1.77	.078	−0.28
BACS symbol coding T-score[1]	30.28 (13.48)	32.18 (11.12)	−0.94	.352	−0.16
MSCEIT-ME T-score	40.75 (11.64)	40.36 (12.58)	0.20	.843	0.03

[1]Adjusted for unequal variances

APS = Attenuated Psychosis Symptoms

BACS = Brief Assessment of Cognition in Schizophrenia

GAF = Global Assessment of Functioning

GF = Global Functioning

HVLT = Hopkins Verbal Leaning Test

MSCEIT-ME = Mayer-Salovey-Caruso Emotional Intelligence Test Managing Emotions Subscale

PANSS = Positive and Negative Syndrome Scale for Schizophrenia

WRAT = Wide Range Achievement Test