Published in final edited form as:
Schizophr Res. 2010 July ; 120(1-3): 95–100. doi:10.1016/j.schres.2010.04.007.

Cannabis Use Disorders in Schizophrenia: Effects on Cognition and Symptoms

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Abstract

Objective—Despite the controversy surrounding the possible causal link between cannabis use and the onset of schizophrenia (SZ), data seeking to elucidate the effect of cannabis use disorders (CUD) on the clinical presentation of SZ have produced mixed results. Although several studies have suggested that CUD in patients with SZ may be associated with variation in cognitive function, clinical presentation and course of illness, the effects have been inconsistent.

Methods—We retrospectively ascertained a large cohort (N = 455) of SZ patients with either no history of a CUD (CUD−; N=280) or a history of CUD (CUD+; N=175). Groups were initially compared on key demographic variables including sex, race, age, age at onset of SZ, parental socioeconomic status, premorbid IQ, education level and global assessment of functioning. Covarying for any observed differences in demographic variables, we then compared groups on lifetime measures of psychotic symptoms as well as a brief battery of neurocognitive tests.

Results—Compared to the CUD− group the CUD+ group demonstrated significantly better performance on measures of processing speed (Trail Making Test A and B), verbal fluency (animal naming) and verbal learning and memory (California Verbal Learning Test). Moreover, the CUD+ group had better GAF scores than the CUD− group.

Conclusions—Collectively, these findings suggest that SZ patients with comorbid CUD may represent a higher functioning subgroup of SZ. Future prospective studies are needed to elucidate the nature of this relationship.

Compared to the general population, patients diagnosed with schizophrenia (SZ) have been reported to have a two-fold increase in rates of cannabis use disorders (CUD) (Arseneault et al 2004; Buckeley et al 2009). While several epidemiological studies from around the world

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consistently estimate a lifetime prevalence rate of ~8% for CUD in the general population (Agrawal & Lynskey 2007; Moore et al 2007), a recent metaanalysis of 35 studies from 16 countries indicated that the median rate of lifetime CUD was 27.1% in patients diagnosed with SZ (Koskinen et al 2009). Although several longitudinal studies have suggested a causal relationship between cannabis use and SZ (Andreasson et al 1987; Fergusson et al 2003; Henquet et al 2005; Stefanis et al 2004; van Os et al 2002; Weiser et al 2002; Zammit et al 2002) it has been suggested that cannabis use may only represent a risk factor for SZ in individuals with an underlying predisposition for psychiatric illness (Arendt et al 2005; Arendt et al 2008; Arseneault et al 2004).

Despite the controversy related to the causal relationship between CUD and SZ, several lines of research suggest that SZ patients with comorbid CUD may represent a clinically distinct subgroup of SZ patients. To date, the most notable findings in this area have been reports that SZ patients with a history of CUD (CUD+) have less severe cognitive deficits than SZ patients without comorbid CUD (CUD−) (Jockers-Scherubl et al 2007; Joyal et al 2003; Kumra et al 2005; Sevy et al 2001; Sevy et al 2007; Stirling et al 2005).

One potential explanation for these findings is that that better cognitive function may represent a risk factor for the development of CUD in patients with SZ. Specifically, the presence of CUD in patients with SZ may be a reflection of the patients' ability to competently engage in social interaction which, in turn, may be a reflection of more intact cognitive functioning. Indeed, several studies of patients with SZ have demonstrated a relationship between neurocognitive performance and interpersonal skills. For example, better performance on measures of verbal skill has been associated with both better interpersonal skills (Addington & Addington 1999; 2000) and better community social functioning (Cohen et al 2006). Moreover, Harvey and colleagues (2009) recently reported that verbal skills were among the strongest predictors of performance-based measures of functional capacity. These authors reported that processing speed accounted for 17%, 24% and 27% of the total variance in performance on the UCSD Performance-Based Skills Assessment Battery, Social Skills Performance Assessment and Specific Level of Function Scale, respectively. Thus, the observed differences in cognitive function between CUD+ and CUD− patients may be reflecting overall differences in social functioning.

Although less consistent, differences in the clinical characteristics of SZ patients with and without comorbid CUD have also been reported. The most consistent of these findings indicate that CUD+ patients have an earlier age at onset of SZ relative to CUD patients (Arendt et al 2005; Barnes et al 2006; Green et al 2004; Hambrecht et al 2000; Veen et al 2004) although not all studies agree (Sevy et al 2001; Cantor-Graae et al 2001). Studies seeking to elucidate the relationship between CUD and other illness related factors including clinical symptoms have also been reported with mixed results. Although some studies have found elevated levels of positive symptoms in SZ patients with CUD relative to SZ patients without CUD (Caspari 1999; Degenhardt et al 2007; Grech et al 2005), other studies have found no difference (Arias et al 2002; Green et al 2004). With regard to negative symptoms, while most studies have reported no difference (Caspari 1999; Grech et al 2005; Stirling et al 2005), many others have reported decreased levels of negative symptoms (Compton et al 2004; Koskinen et al 2009; Peralta & Cuesta 1992) in SZ patients with CUD relative to those without CUD.

Although no clear explanation of the inconsistencies in the data relating CUD to the clinical characteristics of SZ is currently available, it is likely that they are related to the lack of control of potentially confounding variables (Fergusson et al 2003; Macleod et al 2004). Specifically, cannabis use disorders in the general population may be more common among males, minority groups, low socioeconomic groups, those with a family history of psychotic illness (Arendt et al 2005) and those with lower IQ (Arseneault et al 2004) and educational attainment (Chen et

al 2006; Mortensen et al 2005). Because the course of illness in SZ has also been shown to vary as a function of many of these same variables (MacDonald & Schulz 2009), it is critical to control for these potential confounds when making comparisons among SZ patients with and without CUD. Perhaps due to the relatively small samples utilized in these prior studies, few studies have adequately addressed these issues (see Henquet et al 2005 for review).

The present study was therefore designed to assess differences in the clinical characteristics of SZ patients with and without CUD. Specifically, we compared SZ patients with and without a history of CUD across a series of demographic variables and then utilized any observed differences in these variables as covariates in analyses designed to assess the relationships between neurocognitive function, lifetime psychosis and CUD.

METHOD

Sample

The sample included 455 patients with SZ or schizoaffective disorder (SAD) recruited from The Zucker Hillside Hospital (ZHH), a division of the North Shore-Long Island Jewish Health System, in Glen Oaks, N.Y. All subjects provided written informed consent to a protocol approved by the Institutional Review Board of the North Shore-Long Island Jewish Health System (The Genetics of Psychiatric Disorders; PI: AKM). Inclusion in the study required that the patient have a clinical diagnosis of any psychotic disorder, were between the ages of 18 and 65 with no history of neurological disorders, major CNS trauma, no recent (within 1 month) substance abuse or dependence and an estimated premorbid IQ of greater than 70. From this full sample all patients with a diagnosis of SZ or SAD were selected and of these 175 subjects carried a comorbid diagnosis of cannabis abuse (N=51) or cannabis dependence (N=124).

Clinical Assessment

Each subject was assessed with the Structured Clinical Interview for the DSM-IV (SCIDIV) administered by trained and reliable raters. Information obtained from the SCID was supplemented by a review of medical records and interviews with family informants when possible, and compiled into a narrative case summary. Primary and secondary diagnoses were then determined by a consensus among a minimum of three expert diagnosticians from the ZHH faculty.

Because symptom severity often varies during the course of illness, lifetime ratings rather than cross-sectional ratings were used (Craddock & Owen 2006; Levinson & Mowry 1991). Lifetime symptom ratings were derived from SCID data and included ratings on three domains of psychotic symptoms (positive, negative and disorganized), which were obtained by summing the scores for each symptom within a domain such that the negative symptom rating included ratings on avolition, alogia and affective flattening (DeRosse et al 2006), the positive symptom rating included ratings on delusions (referential, paranoid, grandiose, somatic, control, thought broadcasting, bizarre, and other delusions) and hallucinations (auditory, visual, tactile and other hallucinations) (DeRosse et al 2007) and the disorganization symptom rating included ratings on disorganized speech and disorganized behavior (DeRosse et al 2008). Ratings on each of the items were recorded based on the subject's report during the interview as well as the medical record and other available sources and were rated on a continuous scale where 1=absent, 2=subthreshold and 3=present.

Neurocognitive Assessment

Participants were administered a battery of standardized cognitive measures comprised of measures of verbal skill (California Verbal Learning Test (CVLT)-Abridged; Controlled Oral Word Association Test (COWAT), Animal Naming) and processing speed (Wechsler Adult

Intelligence Test-Revised (WAIS-R)-Digit Span; Trail Making Part A & B). Following common practice in the psychiatric literature (Keefe et al 2005), we estimated premorbid IQ using the Wide Range Achievement Test-Third Edition-Reading Subtest (WRAT-3). WRAT-3 is a test that assesses single word reading skill which, like command of general knowledge and vocabulary, is particularly resistant to the effects of deterioration associated with brain disease and is considered an estimate of pre-morbid IQ in patient populations.

Statistical Analyses

All analyses were carried out comparing SZ patients without comorbid CUD (CUD−) to SZ patients with CUD (CUD+). Initially, groups were compared on demographic variables including sex, race, parental socioeconomic status (PSES: Hollingshead 1975) and family history of psychotic illness using Chi square analyses. Comparison of groups on current age, age at onset of SZ, global assessment of functioning (GAF) score, illness duration, premorbid IQ (as measured by WRAT-3) and education level were carried out using t-tests. Because such variables have been shown to vary in relation to both CUD in the general population and the clinical characteristics of patients with SZ, any demographic variable that was shown to differentiate among groups was used as a covariate in the analysis comparing CUD+ and CUD − groups on symptom and neurocognitive domains. Comparison of groups on lifetime severity of positive, negative and disorganized symptoms was carried out using an ANCOVA that covaried for any differences observed in demographic variables. Finally, comparison of groups on neurocognitive domains was carried out using a MANCOVA that covaried for any differences observed in demographic or symptom variables.

RESULTS

Comparison of CUD + and CUD− groups on demographic variables revealed a significant sex difference with a higher proportion of males in the CUD+ group relative to the CUD− group (=34.86; p<0.001). No significant differences were found in racial composition, PSES or family history of psychotic illness. Comparison of groups on GAF score at time of assessment revealed a significant difference between groups (t=2.754, p=0.006) with the CUD+ group having significantly better functioning than the CUD− group (41.30±14.82 vs. 37.33±14.56, respectively). No significant differences were observed on other demographic variables. Comparison of groups on lifetime severity of positive, negative and disorganized symptoms, which covaried for observed differences in sex and GAF score between the two groups, revealed no significant differences between groups on any of the symptom domains. These data are shown in Table 1.

Comparison of the CUD+ and CUD− groups on neurocognitive measures, carried out using a MANCOVA that covaried for the observed differences in sex and GAF score between the two groups, revealed a significant overall group difference (F=3.30, df=7, 228, p=0.002). Specifically, SZ patients with a history of CUD performed significantly better than the CUD − group on Trail Making Part A (F=6.14, df=1, 228, p=0.014), Trail Making Part B (F=11.54, df=1, 228, p=0.001, Animal Naming (F=9.43, df=1, 228, p=0.002) and the CVLT (F=8.84, df=1, 228, p=0.003). Only the latter 3 tests, however, remained significant after correction for multiple testing. The mean scores on all neurocognitive measures for both the CUD+ and CUD − groups are shown in Table 2.

Because patients with schizoaffective disorder (SAD) may have a different neurocognitive profile than patients with schizophrenia (Cheniaux et al. 2008) we conducted a follow-up analysis to assess whether excluding the SAD's would alter the present findings. This analysis yielded the same findings as the analysis of the full group.

DISCUSSION

The results of the present analysis suggest that CUD in patients with SZ is associated with better performance on measures of processing speed and verbal skills. These data are consistent with prior reports indicating that SZ patients with a history of CUD have less severe cognitive deficits than SZ patients without comorbid CUD (Jockers-Scherubl et al 2007; Kumra et al 2005; Sevy et al 2007; Stirling et al 2005). The observed relation between CUD and verbal skills is likely related to the relationship between verbal ability and both interpersonal skills (Addington & Addington 1999; 2000) and community social functioning (Cohen et al 2006) previously observed in patients with SZ. Specifically, the presence of CUD in patients with SZ may be a reflection of the patients' ability to competently engage in social interaction. This is consistent with the recent findings of Harvey and colleagues (2009) who reported that verbal skills were among the strongest predictors of performance-based measures of functional capacity. Similarly, these authors also reported that processing speed accounted for a substantial portion of the total variance in performance on measures of functioning. Thus, it is likely that the observed differences in cognitive function between CUD+ and CUD− patients may be reflecting overall differences in social functioning. Further support for this relationship is provided by the current findings of better global functioning in SZ patient with comorbid CUD. Additional data are needed, however, to elucidate how and why the social environment of patients with SZ may increase the odds of coming in contact with cannabis.

The present findings also suggest that CUD in patients with SZ may not differentially affect the severity of illness as measured by clinical symptomatology. Studies seeking to elucidate the relationship between CUD and other illness-related factors including clinical symptoms have been inconsistent. Although no clear explanation of the inconsistencies in the data relating CUD to the clinical characteristics of SZ is currently available, it is has been suggested that the inconsistencies may be due to the lack of control of potentially confounding demographic variables (Fergusson et al 2003; Macleod et al 2004). Specifically, SZ and CUD share many of the same risk factors including being more common among males, minority groups, low socioeconomic groups, lower IQ and decreased educational attainment. Due to the relatively small sample sizes utilized in previous studies, however, most were not able to adequately control for these potential confounds. In the present study, however, the CUD+ and CUD− groups were well matched on virtually all of the demographic variables assessed. The fact that our groups were well-matched on these variables may also account for our lack of findings relating CUD to the age at onset of SZ. Contrary to prior reports indicating that CUD+ patients have an earlier age at onset of SZ relative to CUD patients, we found that the age at onset of SZ did not differ significantly between the CUD+ and CUD− groups.

It should be noted that our data are limited by several factors. Moreover, collection of neurocognitive data occurred at a single time point and in the context of a large study designed to study the genetics of psychiatric disorders. Thus, there was no uniformity in duration of time since last use of cannabis. Although none of the CUD+ patients had been using cannabis at the time of the assessment, the time since last use varied amongst patients. Recent data, however, have suggested that the effects of cannabis on cognitive function are relatively short lived. Specifically, Pope and colleagues (2001) found that decrements in cognitive performance associated with cannabis use were minimal 24 hours after use and no longer evident after 28 days of abstinence. In the present study, none of the CUD+ patients had used cannabis in the preceding 24 hours and fewer than 10% reported having used cannabis in the month preceding the assessment. Thus, it seems unlikely that the present results reflect the acute effects of cannabis exposure. Moreover, although we did not use a healthy control group as a baseline with which to compare the performance of our SZ groups, the levels of impairment observed are comparable to those reported in other SZ samples. Finally, although determination of lifetime clinical ratings was bolstered by the availability of substantial chart histories on most

of the patients, the scale used for symptom ratings was limited in its ability to assess severity of specific symptoms over the entire course of illness or to detect subtle differences between levels of symptom severity.

Thus, future prospective studies seeking to assess such subtle differences using measures of current symptom severity are needed. Despite these limitations, the present findings suggest that SZ patients with comorbid CUD may represent a higher functioning subgroup of SZ. Future large-scale, prospective studies are needed to elucidate the nature of this relationship.

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Table 1

Comparison of schizophrenia patients with (CUD+) and without (CUD−) cannabis use disorders on demographic and symptom variables. Scores provided for quantitative variables represent the mean and standard deviation.

	CUD+	CUD−	Statistic	P value
% Female	12.57%	38.21%	$\chi 2=34.86$	**<0.001**
Race			$\chi 2=0.09$	0.95
White	45.71%	44.64%		
Black	38.86%	38.93%		
Other	15.43%	16.43%		
PSES*			$\chi 2=1.73$	0.63
SPI 1 or 2	18.33%	15.50%		
SPI 3	34.17%	29.50%		
SPI 4	19.17%	23.00%		
SPI 5	28.33%	32.00%		
Family History (% Positive)	21.48%	22.87%	$\chi 2=0.75$	0.80
GAF Score	41.30 ±14.82	37.33 ± 14.56	t=2.75	**0.006**
Current Age	36.76 ± 10.54	37.70 ± 10.72	t=0.91	0.36
Age at Onset of SZ	19.68 ± 5.18	20.54 ± 5.89	t=1.26	0.19
SZ Illness Duration	16.91 ± 10.35	17.16 ± 11.16	t=0.24	0.81
Premorbid IQ (WRAT-3)	93.36 ± 13.42	92.48 ± 14.07	t=0.60	0.55
Education Years	12.43 ± 2.07	12.72 ± 2.18	t=1.25	0.21
Positive Symptoms	23.77 ± 4.72	23.16 ± 4.69	F=1.88	0.17
Negative Symptoms	5.46 ± 2.17	5.71 ± 2.20	F=3.12	0.08
Disorganized Symptoms	5.01 ± 1.89	5.08 ± 1.90	F=0.07	0.79

* Social Position Index (Hollingshead, 1975)

Table 2

Comparison of schizophrenia patients with (CUD+) and without (CUD−) cannabis use disorders on measures of processing speed and verbal skill. Scores provided represent the mean and standard deviation.

Domain	Measure	CUD+	CUD−	F Statistic	p value
Processing Speed	Trail Making Part A (Time)	42.74 ± 20.36	50.14 ± 23.97	6.14	**0.01**
	Trail Making Part B (Time)	135.31 ± 76.74	170.02 ± 87.57	11.54	**<0.001**
	Digits Forward	5.84 ± 1.23	5.78 ± 1.32	0.003	0.95
	Digits Backward	4.02 ± 1.30	4.01 ± 1.11	0.005	0.94
Verbal Skills	Animal Naming	17.10 ± 6.07	14.79 ± 4.93	9.43	**0.002**
	CVLT	36.89 ± 11.28	33.17 ± 10.37	8.84	**0.003**
	COWAT	33.60 ± 11.87	31.53 ± 11.27	2.08	0.15