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Psychopharmacological comparison of schizophrenia spectrum disorder with and without cannabis dependency

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ABSTRACT

Background: Although incidence of schizophrenia is higher among cannabis users and marijuana is the most common abused drug by adolescents, etiological linkage between schizophrenia and cannabis use is still not clarified. Clinical experiences suggest that regular cannabis user can show similar psychotic episode to schizophrenic disorders but it is still unclear if chronic cannabis use with schizophreniform disorder is a distinct entity requiring special therapy or it can be treated as classical schizophrenia. There are no data available on the comparison of pharmacotherapy between schizophreniform patients with and without cannabis use.

Methods: Clinical data of 85 patients with schizophrenia spectrum disorder were analyzed retrospectively. Cannabis use was not reported by 43 persons (Cnbs0 subgroup) and 42 patients used regularly cannabis during at least 1 year (Cnbs1 subgroup). Comparison of anamnesis, family history, social-demographic condition, positive and negative symptoms, acute and long-term therapies recorded by clinical interviews was performed with chi square tests, logistic binary regression and t-tests using SPSS 13.0 for Windows software.

Results: Men were over-represented in cannabis dependent group while mean age was lower among them compared to Cnbs0 subgroup. Prevalence of suicidal attempt was increased in men without cannabis use ($OR = 5.25$, $p = 0.016$). Patients without cannabis use spent more time in hospital ($p = 0.026$) and smoking was more frequent among them ($OR = 1.36$, $p = 0.047$). The chance to get olanzapine for acute therapy and aripiprazol for long term therapy was more than two fold in Cnbs1 subgroup ($OR = 2.66$, $OR = 3.67$, respectively). However, aripiprazol was used for acute therapy with significantly lower risk in Cnbs1 subgroup ($OR = 0.47$, $p = 0.023$). Olanzapine was administered for long term therapy in a higher dose to Cnbs0 patients ($p = 0.040$). Also higher dose of risperidon LAI was used in women without cannabis dependency compared to women of Cnbs1 subgroup ($p = 0.020$). Positive and negative symptoms and family history did not differ significantly between the two subgroups.

Conclusion: Although symptom profile was similar, hospitalization time, suicidal anamnesis, smoking habit and also dosage, intensity and lasting of therapy were different between the two subgroups. Further prospective studies are required for the investigation of the clinical and molecular background of this discrepancy in order to determine a relevant protocol of prevention and treatment of the chronic cannabis use related psychotic disorder.

1. Introduction

Marijuana (cannabis) is the most commonly abused drug by adolescents and young adults (accounting for more than 50% of all drug abuse according to NIDA) and most frequently abused by people with schizophrenia or other psychotic disorders (Linszen et al., 1994; Bersani et al., 2002). An increasing number of studies suggest that cannabis use is associated with the subsequent development of psychotic symptoms later in life, even after applying a range of controls for confounding factors and various statistical approaches in analysis (Andreasson et al., 1987; Arseneault et al., 2002; van Os et al., 2002). Recent meta-analyses suggest that a 1.4 times higher risk is estimated to have a psychotic outcome in ever user and cannabis can account for 8–14% of schizophrenia cases (Henquet et al., 2005; Moore et al., 2007). By now several data support the link between psychosis and cannabis use. Firstly, an earlier age at onset of psychosis for patients with a history of cannabis use was reported (Veen et

Abbreviations: CB1, cannabinoid receptor 1; CGI-S, Clinical Global Impression Scale; CGI-I, Clinical Global Improvement Scale; Cnbs, cannabis; HPDC, haloperidol decanoate; LAI, long acting injections; OR, odds ratio.

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al., 2004; Green et al., 2005; Barnes et al., 2006; Gonzalez-Pinto et al., 2008) and similarly, individuals with a high risk for developing psychosis (as indicated by the presence of subsyndromal psychotic symptoms, positive family history, and recent deterioration in global function) have higher rates of psychotic outcomes associated with cannabis (Miller et al., 2001; Kristensen and Cadenhead, 2007; Arendt et al., 2008; Corcoran et al., 2008). Secondly, the incidence of schizophrenia is higher among cannabis dependents and many studies have demonstrated that substance use typically precede onset of the psychotic disorder, often by several years (Silver and Abboud, 1994; Rabinowitz et al., 1998; Buhler et al., 2002; Green et al., 2005; Mauri et al., 2006). Moreover, Boydell et al. (2006) reported a parallel rise of prevalence of cannabis use and incidence of schizophrenia in South London, UK (Boydell et al., 2006). However, only in a very small proportion of the population exposed to cannabinoids develops a psychotic illness, which suggests that a genetic vulnerability is required instead of a direct association (D'Souza et al., 2009). On the other hand, animal studies and molecular investigations suggest that exogenous cannabinoids can affect normal brain development during adolescent increasing the risk for schizophrenia (Keshavan et al., 1994; Robbe et al., 2001; Fernandez-Espejo et al., 2009) and alteration of endogenous cannabinoid system is reported in several studies (Leweke et al., 1999; De Marchi et al., 2003; Giuffrida et al., 2004; Fernandez-Espejo et al., 2009). In addition, experimental data suggest that stimulation of cannabinoid receptor 1 (CB1) receptors can lead to a facilitation of dopamine release in the mesolimbic system and a dysregulation of dopaminergic activity which is crucial in the pathomechanism of schizophrenia (Pertwee, 2005; Fernandez-Espejo et al., 2009).

There is an intensive discussion in the literature whether cannabis induced psychosis might be a distinct entity with special features or cannabis use can precipitate schizophrenia in those patients with genetic vulnerability (gene–environment interaction). To clarify this question – besides other investigating methods – it is crucial to observe clinical characteristics of cannabis induced psychosis in comparison to other schizophrenic disorders in different study designs. Male gender and young age were associated with increased risk for schizophrenia-spectrum disorder among cannabis user consequently (Arendt et al., 2005; D'Souza et al., 2009; Sugranyes et al., 2009). Comparison of symptoms of chronic psychosis with and without cannabis abuse resulted in conflicting data. While certain results suggested no difference between the two subgroups, others showed that cannabis dependent had less positive thought disorder and fewer negative symptoms (Bersani et al., 2002; Buhler et al., 2002; Boydell et al., 2007). Soyka et al. (2001) reported that patients with current cannabis use had more incoherence, more delusions of reference, fewer delusions of guilt, more visual hallucinations, more First Rank symptoms and less insight (Soyka et al., 2001). Family history of psychotic patients with and without cannabis use was widely investigated. Arendt et al. (2008) reported that children of a mother treated with schizophrenia were at a 5-fold increased risk of developing schizophrenia and a 2.5-fold increased risk of developing cannabis-induced psychosis (Arendt et al., 2008). The risk of a schizophrenia spectrum disorder following a cannabis-induced psychosis and the timing of onset were not associated with familial predisposition (Arendt et al., 2008). Other authors revealed that progression to daily cannabis and tobacco use was associated with an increased risk of onset of psychotic symptoms (Compton et al., 2009).

Pharmacological therapy of cannabis induced psychosis was investigated by two studies. Potvin et al. (2006) reported that quetiapine had significant effect on craving (Potvin et al., 2006), while the effect of clozapine was described as "marked decrease" in cannabis consumption (Zimmet et al., 2000). Neither of them was randomized controlled trials and no data available about the comparison of pharmacological treatment between schizophrenic disorder with and without cannabis use.

The aim of our study was to compare retrospectively the clinical characteristics between schizophrenic disorder with and without chronic cannabis use in a Hungarian first-hospitalized population.

2. Methods

Clinical data were processed retrospectively of 85 patients hospitalized with a schizophrenia spectrum disorder for the first time in the 1st Department of Psychiatry in Nyírő Gyula Hospital and in the Department of Clinical and Theoretical Mental Health in Kutvolgyi Clinical Center, Semmelweis University between 1 January 2007 and 31 December 2009 (standardized electronic system is available from 1 January 2007). Exclusion criteria were age older than 35 year (Sugranyes et al., 2009) and earlier hospitalization at a psychiatric department. Two subgroups were compared based on diagnosis and anamnesis. Patients with psychotic episode without use of any drug in the psychiatric history (ICD-10 F20.X and F23.X) were categorized as $Cnbs_0$ (n = 43), while $Cnbs_1$ subgroup was created by those psychotic subjects with anamnesis of daily consumption during at least 1 year of cannabis (n = 42). These patients reported app. 0.5–1 g cannabis use per a day. Current cannabis use was verified by a urine test at the admission to the department. Diagnosis was determined by psychiatrists based on clinical interview according to the DSM-IV criteria. Clinical data were collected from electronic medical documentation of patients about anamnesis, family history, social-demographic condition, symptoms and psychiatric state, acute and long-term therapies. The state of patient at admission and emission was recorded with the Clinical Global Impression Scale (CGI-S) and the Clinical Global Improvement Scale (CGI-I), respectively.

Comparison of categorical variables was computed with chi square test and odds ratios were estimated with binary logistic regression. In case of continuous variable *t*-test and ANOVA tests were performed adjusted by age and gender. Results were accepted as significant if p-value was less than 0.05 and as a trend between 0.05 and 0.08. All statistical tests were performed by SPSS 13.0 for Windows software.

3. Results

Age and gender were significantly different between $Cnbs_0$ and $Cnbs_1$ subgroups. Mean age of subjects with cannabis dependency was significantly lower ($p = 0.0001$) and more men were presented among them compared to $Cnbs_0$ subgroup (OR = 2.28, $p = 0.007$). Cannabis dependents were more qualified ($p = 0.001$) and had better social status ($p = 0.002$). Patients of suicidal attempt were more than fivefold higher in men without cannabis use (OR = 5.25, $p = 0.016$). Hospitalization time was significantly longer in case of patients without cannabis dependency compared to $Cnbs_1$ subgroup ($p = 0.026$). The chance to smoke at least 10 cigarettes per day was higher among $Cnbs_0$ patients (OR = 1.36, $p = 0.047$). Prevalence of psychotic symptoms did not differ significantly between the two subgroups. Most common symptom was incoherency in $Cnbs_0$ and hallucination in $Cnbs_1$ subgroup. Surprisingly, similar prevalence of aggression was observed in the two subgroups (Table 1 and Fig. 1). Mean scores of CGI-I and CGI-S were also similar in the two subpopulations.

We made a comparison of acute and long term therapies between the two subgroups. In our sample aripiprazol and ziprasidon were not used for the acute therapy of cannabis dependent patients at all. The chance to get olanzapine for acute therapy and aripiprazol for long term therapy was more than twofold in $Cnbs_1$ subgroup (OR = 2.66, $p = 0.048$; OR = 3.67, $p = 0.052$, respectively) (Table 2). Typical and atypical antipsychotics were applied at the same ratio in both populations ($p = 0.78$).

Mean doses of administered antipsychotics were higher in acute therapy of $Cnbs_0$ patients except in case of olanzapine and cisordinol. Higher dose was used of quetiapine in patients without cannabis dependency compared to $Cnbs_1$ subgroup with a strong trend ($p = 0.053$). Although difference of mean dose of clonazepam was not significant between the two subgroups in the whole population, men get higher dose with a strong trend in $Cnbs_1$ subgroup

Table 1
Anamnesis and socio-demographic characteristics of study population.

	$Cnbs_0$ ($n=43$)	$Cnbs_1$ ($n=42$)	*p*-value (O.R.;95%C.I.)
Age (mean ± S.D.)	31.3 ± 3	24.45 ± 4.4	**0.0001**
Gender (n)			
Males	22 (51%)	33 (78%)	**0.007**
Females	21 (48%)	9 (21%)	(2.28; 1.18–4.38)
Positive psychiatric FH (n)	10 (23%)	7 (17%)	ns
Death of parents (n)	10 (23%)	4 (0.9%)	ns
Suicidal attempt (n)	11 (26%)	6 (14%)	ns
In men	7 (0.9%)	2 (0.03%)	**0.016** (5.25; 1.20–22.97)
Smoking (n)	23 (53%)	19 (45%)	**0.047** (1.36; 0.98–1.89)
Alcohol (n)	12 (28%)	13 (31%)	ns
Education (n)			
No qualification	27	18	**0.001**
Technical school	10	7	
High school	5	16	
Degree	1	1	
Employment (n)			
No	31	24	**0.002**
Temporary	1	8	
Permanent	7	1	
Institution	4	9	
Lifestyle (n)			
Homeless	6	1	ns
Single	3	10	
Married/couple	8	0	
Living with parents	25	29	
Institution	1	2	

FH, family history; O.R., odds ratio; C.I., confidency intervallum.

($p=0.053$) compared to the men of $Cnbs_0$ subpopulation (Table 3, Fig. 2).

In case of long term therapy patients with cannabis dependency get higher dose of clozapine and alprazolam. Olanzapine was administered to patients without cannabis use in a significantly higher dose compared to $Cnbs_1$ subgroup ($p=0.040$), although mean dose of alprazolam was higher in the latter subgroup with a trend ($p=0.076$) (Table 3, Fig. 2).

Antipsychotic LAI was applied with higher chance in $Cnbs_1$ subpopulation (OR = 1.68, $p=0.042$), however, haloperidol-decanoate depot injection was not used among them at all. There was no significant difference between the use of typical and atypical depot injections ($p=0.67$). Mean dose of risperidon (computed for 6 months) was almost significantly higher in patients without cannabis dependency dose ($p=0.063$) and significantly higher in women without cannabis

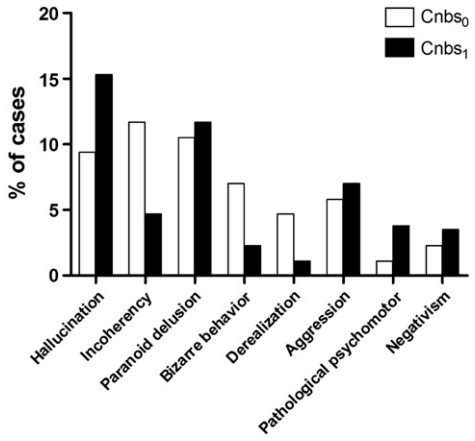

Fig. 1. Prevalences of symptoms in the two subgroups. Differences of symptom prevalence were not significant between patients with ($Cnbs_1$) and without ($Cnbs_0$) cannabis use.

Table 2
Estimated risk for apply of different antipsychotics in $Cnbs_1$ subgroup.

	OR for therapy in $Cnbs_1$ subgroup	95%C.I.	*p-value*
Acute therapy			
Olanzapine	2.66	0.75–9.37	**0.048**
Aripiprazol	0.47	0.37–0.59	**0.023**
Long term therapy			
Aripiprazol	3.67	0.59–22.86	**0.052**
Antipsychotic LAI	1.68	0.94–3.01	**0.042**
HPDC	0.47	0.37–0.59	**0.023**

Only significant odds ratios are presented int he table. LAI, long acting injection; HPDC, haloperdiol-decanoate.

dependency compared to women of $Cnbs_1$ subgroup ($p=0.020$) (Table 2).

4. Discussion

We made a detailed comparison of patients with schizophrenic disorder with and without chronic cannabis use based on retrospective clinical data. Our results suggest that besides similar symptom profiles there are significant differences between the two subgroups concerning mean age and gender pattern, suicidal anamnesis, smoking habits, hospitalization time and pharmacotherapy. These alterations could be a good base to help clinicians place the cannabis related schizophrenic disorder in the clinical classifications.

Table 3
Acute and long term therapies of patients with ($Cnbs_1$) and without cannabis use ($Cnbs_0$).

	$Cnbs_0$	$Cnbs_1$	*p*-value
Acute treatment (mg/day)			
Haloperidol	16.63 ± 11.18 ($n=8$)	14.27 ± 7.82 ($n=13$)	ns
Risperidon	5.50 ± 4.03 ($n=10$)	4.22 ± 1.85 ($n=9$)	ns
Olanzapine	24.38 ± 15.45 ($n=8$)	26.50 ± 33.23 ($n=2$)	ns
Quetiapine	**600.0 ± 316.22 ($n=8$)**	**153.33 ± 214.55 ($n=3$)**	**0.053**
Aripiprazol	30.0 ± 0.00 ($n=5$)	–	–
Clozapin	300.0 ± 100 ($n=3$)	300 ± 0.0 ($n=1$)	ns
Ziprasidon	160.0 ± 0 ($n=2$)	–	–
Alprazolam	2.34 ± 1.28 ($n=7$)	1.81 ± 0.89 ($n=4$)	ns
Clonazepam	3.33 ± 1.83 ($n=18$)	4.25 ± 2.01 ($n=16$)	ns
In men	**2.94 ± 1.89 ($n=8$)**	**4.69 ± 1.88 ($n=13$)**	**0.053**
Diazepam	40.0 ± 0.0 ($n=2$)	33.33 ± 5.77 ($n=3$)	ns
Long term therapy (mg/day)			
Aripiprazol	30.0 ± 15.35 ($n=6$)	15.0 ± 0 ($n=1$)	ns
Clozapine	162.50 ± 194.45 ($n=2$)	175.0 ± 139.19 ($n=3$)	ns
Olanzapine	**19.29 ± 1.89 ($n=7$)**	**13.61 ± 6.96 ($n=10$)**	**0.040**
Quetiapine	633 ± 239.79 ($n=9$)	440.0 ± 341.23 ($n=5$)	ns
Risperidon	3.88 ± 1.35 ($n=8$)	3.38 ± 1.19 ($n=13$)	ns
Alprazolam	**1.30 ± 0.51 ($n=11$)**	**1.90 ± 0.742 ($n=5$)**	**0.076**
Clonazepam	3.36 ± 1.95 ($n=11$)	2.80 ± 2.15 ($n=10$)	ns
Antipsychotic LAI (n)	15 (34%)	8 (19%)	ns
Risperidon (mg/6 months)	**578.57 ± 56.69 ($n=7$)**	**430.00 ± 178.88 ($n=5$)**	**0.063**
In women	**600 ± 0.0 ($n=2$)**	**250 ± 70.71 ($n=2$)**	**0.020**
Zuclopenthixol (mg/6 months)	1733.33 ± 611.01 ($n=3$)	2400.0 ± 0.0 ($n=2$)	ns
Flupenthixol (mg/6 months)	160.0 ± 0.0 ($n=1$)	180.0 ± 84.85 ($n=2$)	ns
HPDC (mg/6 months)	480 ± 164.31 ($n=5$)	–	–
Hospitalization time (day)	**35.72 ± 26.96**	**23.02 ± 19.28**	**0.026**
CGI-S	4.98 ± 0.55	5.22 ± 0.51	ns
CGI-I	2.51 ± 0.79	2.59 ± 0.57	ns

LAI, long acting injection; CGI-S, Clinical Global Impression Scale; CGI-I, the Clinical Global Improvement Scale, HPDC, haloperidol-decanoate.

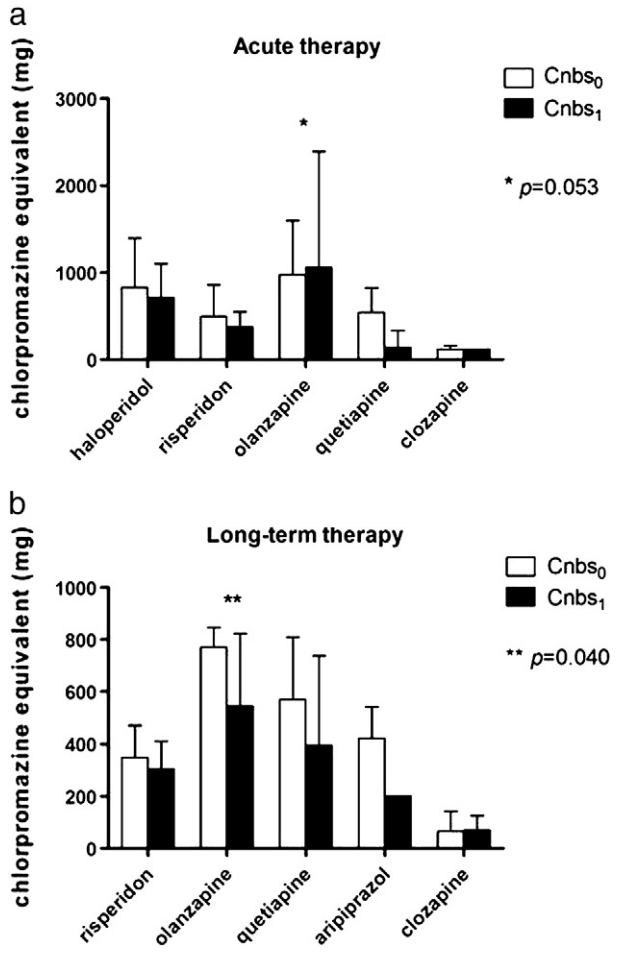

Fig. 2. Differences of antipsychotic doses between the two subgroups. a. Quetiapine was administered for acute therapy in lower dose to patients with cannabis abuse ($Cnbs_1$) with a strong trend. b. Cannabis dependents get significantly lower dose of olanzapine for long-term therapy than patients without cannabis dependency ($Cnbs_0$). Applied doses are presented by chlorpromazine equivalents (Woods, 2003).

One important difference between cannabis related schizophrenic disorder and schizophrenia is the age of onset. Earlier first onset of psychotic episode in cannabis dependents is reported comparing other psychotic disorder in several studies (Arendt et al., 2005; Compton et al., 2009; Sugranyes et al., 2009). Our findings are in accordance with this association although in our sample those patients, who had first hospitalization instead of first episode, were involved. This inclusion criterion was designed because the major point of this study was to assess chronic cannabis dependent with definitive schizophrenic disorder and not with transient psychotic episode which could have occurred in the anamnesis without hospitalization. Furthermore, results from a prospective study suggest that not in all cases but approximately half of the subjects developed a schizophrenia spectrum disorder at some time after the cannabis-induced psychosis (Arendt et al., 2008). Onset of the first episode at younger age is widely discussed but still remained an unsolved question. Because cannabis use is predominantly associated with adolescent age, it can be possible that cannabis can activate schizophrenia at earlier lifetime in the vulnerable individuals (Fernandez-Espejo et al., 2009).

Gender differences between the two subgroups have been described in previous publications too. Although both sexes are represented at the same ratio in schizophrenia population, an earlier onset is observed among men than in women (Leung and Chue, 2000; Mueser and McGurk, 2004; Barnes et al., 2006). In harmony with the literature a higher number of men can be observed in cannabis dependent in our study (Barrigon et al.; Arendt et al., 2005; Boydell et al., 2007; Sugranyes et al., 2009). Increased suicidal risk among patients even among men with schizophrenia compared to general population is a well known phenomenon and patients with schizophrenia and substance use have a history of more suicidal attempts (Soyka et al., 2001; Auquier et al., 2007). In our study cannabis related schizophrenic disorder was associated with lower occurrence of suicidal attempt among men compared to men without cannabis use. However, as mean age of cannabis dependent was younger, it is likely that lifetime prevalence can be the same.

In the point of medication, multiple differences were shown between the two subgroups. The hospitalization time was shorter for cannabis dependent which can be associated with previously reported results, in which cannabis induced psychosis retrograded more quickly than other psychosis (Chaudry et al., 1991; Basu et al., 1999; Wiley et al., 2008). Better therapy response can also explain this observation, moreover, because lower doses of antipsychotics were administered to patients with cannabis use compared to others. In the literature most of data focused on clozapine and its beneficial effect was confirmed by a clinical and also by a CB1 receptor binding study (Drake et al., 2000; Sundram et al., 2005). Sex and age differences were demonstrated in a special investigation where subchronic clozapine treatment decreased CB1 receptor density in female rat brain but did not remain significant in males and in adolescents (Wiley et al., 2008). In our sample clozapine was not used more commonly among cannabis related schizophrenic disorder, however, other members of the same pharmacological group (dibenzodiazepines) with similar chemical character to clozapine, namely, quetiapine and olanzapine were administered with significantly lower doses to cannabis dependent in acute and long-term treatments, respectively. To interpret these data, it is crucial to clarify that in our measurements the major aim of the therapy was the elimination of psychotic symptoms and not the treatment of cannabis dependency but the outcome of change in cannabis consumption was not recorded. Our findings that aripiprazol was more commonly chosen for long-term treatment of cannabis related schizophrenic disorder than of others were in accordance with a recently published study in which chronic treatment with aripiprazol induced cannabinoid receptor 1 gene (Cheng et al., 2008). Furthermore, patients in the cannabis dependent group needed a lower dose of risperidon long-acting injection. The fact that long acting injections in general were applied more commonly among cannabis dependents can be associated with a weaker adherence as it was demonstrated in a prospective study (Miller et al., 2009). These data may implicate a more dibenzodiazepine-sensitive psychosis with weaker adherence in the case of cannabis dependent than in schizophrenia. It may suggest that a disorder of the endocannabinoid system in schizophrenia without cannabis abuse can be differed from stimulated endocannabinoid system by exogenous cannabinoids. Nevertheless anxiolytics were used in higher dose in $Cnbs_1$ patients than in others but no data were available in the literature with regard the effects of anxiolytics in cannabis dependents. Comparison of clinical states between admission and emission by CGI-S and CGI-I points showed that there was no significant difference between the two subgroups. Regarding most of the pharmacological agent used in lower dose during shorter hospitalization time, it suggests that pharmacotherapeutic effect in cannabis dependent patients with schizophreniform disorders can be evaluated objectively better than in non users. A theoretical explanation of this phenomena can be that molecular imbalance in classical schizophrenia may be dependent on more pronounced genetic effect. In contrast, in case of cannabis users disturbance of neurotransmitters can originate principally in environmental factor, namely cannabis use which can be corrected by pharmacotherapy better than in 'endogenous' schizophrenia. Other hypothesis can be a pharmacogenetic difference when enzymes responsible for metabolization of medications can be genetically different between the two subgroups. Further pharmacogenetic studies required clarification of this theory.

The frequencies of positive and negative symptoms were similar in both populations in accordance with some previous data (Boydell

et al., 2007; Arendt et al., 2008). It is noteworthy that prevalence of aggression – which is strongly related to other drug abuse – was also the same in cannabis dependent than in patients with schizophrenia in our sample (Soyka, 2000). One limitation of our study was that cognitive deficits were not investigated in our sample, although results suggested consequently that cannabinoids can influence the learning, short-term memory, working memory, executive function, abstract ability, decision-making and attention (Miller et al., 1977; Hooker and Jones, 1987; Marks and MacAvoy, 1989; Heishman et al., 1990; Leweke et al., 1998; Hart et al., 2001; Ranganathan and D'Souza, 2006). An important characteristic referring to substance dependence like smoking habit was less often among cannabis dependents than in schizophrenia subgroup. Addictive mechanism in schizophrenia is intensively investigated because of increased prevalence of smoking as well as reported cannabis use. An alternative explanation is a self-medication hypothesis suggesting a dysregulated neural signaling of drug reward-patients with schizophrenia that would show an addictive behavior as a primary disease symptom. According to this hypothesis the psychosis-prone individuals are more likely to use cannabis (an association model) or cannabis use increases psychosis-proneness (a causal model) or there is another factor that causes both of them (an indicator-variable model) (Henquet et al., 2005; Schiffman et al., 2005). In contrast, self-medication hypothesis was not supported by the results from a prospective study where cannabis use by patients with schizophrenia predicts an increase in psychotic symptoms, whereas psychotic symptoms do not predict more cannabis use (Degenhardt et al., 2007).

Family history of psychiatric disorders was also similar in the two subgroups. Although recent genetic studies suggested that CNR1 gene can play an important role in development of hebephrenic schizophrenia or therapeutic effects of antipsychotics and also in alcohol dependence, those findings concerning family history are not consistent (Schmidt et al., 2002; Ujike, 2002; Chavarria-Siles et al., 2008; Hamdani et al., 2008; Fernandez-Espejo et al., 2009). In certain studies psychopathological alterations were demonstrated among relatives of patients with cannabis induced psychosis but other results did not confirm this association (Mathers and Ghodse, 1992; McGuire et al., 1995; Basu et al., 1999; Bersani et al., 2002; Chaudry et al., 1991; Rolfe et al., 1993; Nunez and Gurpegui, 2002; Boydell et al., 2007). However, in a recently published study fewer neurological signs were reported among first-episode psychotic patients with a history of heavy cannabis use, suggesting a possible different pathway for psychosis onset (Ruiz-Veguilla et al., 2009).

5. Conclusion

Taken together, in our study certain clinical aspects were different in terms of cannabis related schizophrenia spectrum disorder compared to schizophrenia. These data suggest that besides shared components, vulnerability for cannabis use and schizophrenia and may be also for addictive disorders may have different biological backgrounds, including pharmacogenetic and molecular levels with consequently different pharmacological responses.

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