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Association of smoked cannabis with treatment resistance in schizophrenia

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ABSTRACT

Association of cannabis use with schizophrenia is a well-established finding. Its role in causation, however, is debated. Different studies have found that cannabis use impacts the outcome of schizophrenia and is associated with treatment non-adherence and a higher rate of relapses. In this paper, we investigated the impact of self-reported cannabis use on treatment response in a cohort of schizophrenia patients from Pakistan, a middle-income country. The data was collected from a psychiatric hospital in Khyber Pakhtunkhwa province of Pakistan where cannabis use is prevalent. Clinical evaluation and therapeutic response were established using the Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impressions Scales-Severity (CGI-S) and Improvement (CGI-I) scale. Lack of response to adequate treatment with two trials of antipsychotics was classed as treatment resistance. We compared the treatment-resistant and treatment responsive groups for different variables including cannabis use, age at onset of illness, duration of untreated psychosis and consanguinity. We had data on 230 patients. More than ninety percent of our participants were men. The rate of treatment resistance was over 60%. Ongoing use of cannabis had an association with treatment resistance. We only included cases where treatment adherence was not a problem.

1. Introduction

Schizophrenia is a debilitating neuropsychiatric illness that affects approximately 1% of the population worldwide (Whiteford et al., 2013). It is treated with different classes of antipsychotic drugs (APDs). Approximately 21% of patients are resistant to conventional doses of APD (Wimberley et al., 2016). The treatment-resistant schizophrenia patient is typically treated either with significantly higher doses of APDs, combination therapies or with clozapine. A large number of studies have been undertaken to understand the epidemiology and risk factors associated with treatment-resistant schizophrenia .

Cannabis is the most commonly abused illicit substance with a 4% prevalence worldwide (Degenhardt et al., 2008). High rates of use are reported among patients who have schizophrenia with approximately 43% prevalence (Hartz et al., 2014). Studies have consistently reported an increased risk of psychosis in cannabis users (Bersani et al., 2002; Libuy et al., 2018; Moore et al., 2007). Furthermore, different studies have found an association between cannabis use and poor outcome, treatment non-adherence and increased relapse in schizophrenia (Leeson et al., 2012; Schoeler et al., 2016a, 2016b). An important question is whether concurrent use of cannabis leads to treatment resistance in schizophrenia and whether schizophrenia with cannabis use requires different treatment strategies. In a review, Lazary found that antipsychotics were effective in the treatment of dual diagnosis of schizophrenia and cannabis use (Lazary, 2012). The sample size of the studies reviewed was small. None of the trials they reviewed compared the response in patients with schizophrenia against the ones with the dual diagnosis of schizophrenia and cannabis use. A retrospective observational study of 85 participants found no difference in treatment response in the two groups (Makkos et al., 2011). In a more recent review antipsychotics were found effective in treating psychotic symptoms in patients who along with schizophrenia had cannabis use disorder (Wilson and Bhattacharyya, 2016). In a trial, a group of drug naïve first episode patients with non-affective psychosis was randomized to olanzapine, risperidone, and haloperidol. The patients who used cannabis had an inadequate response to medication in positive and disorganized domains (Pelayo-Terán et al., 2014). In CATIE trial the use of cannabis attenuated the response to medication (Swartz et al., 2008).

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This study excluded patients who were treatment resistant. In an observational study of 2026 patients with first-episode psychosis the subgroup who used cannabis had a higher number of hospital admissions, mediated by a more significant number of antipsychotics prescribed. This implied a antipsychotics treatment failure (Patel et al., 2016). This study did not adjust for poor compliance and other substance use.

In this paper, we describe a cross-sectional study that investigated the impact of self-reported past or current use of cannabis on treatment response in schizophrenia from Pakistan. We obtained a detailed history of cannabis use (quantity, lifetime exposure and use before or after the onset of illness) to investigate this relationship. The study was conducted in North West Frontier Province (now known as Khyber Pakhtunkhwa) of Pakistan where cannabis use is more prevalent because of its proximity to cannabis production areas and trafficking routes.

2. Experimental procedures

The study was approved by the Departmental Ethics Committee (Department of Pharmacy, University of Peshawar, Pakistan).

2.1. Setting

Study was conducted in the Out Patient Department of Sarhad Hospital for Psychiatric Diseases, Peshawar, Khyber Pakhtunkhwa (KPK), Pakistan, which is a 200 bed, medium size tertiary care Psychiatry Hospital. It caters for chronic and severe cases of psychiatric illnesses of the province of KPK and adjoining border areas of Afghanistan. KPK has a total population of 30.52 million. On average 150 patients attend the outpatient Department in a day. Health professionals make the referrals to the hospital but patients and their families can also self-refer. The hospital provides medication and people usually return for follow-up visits.

2.2. Participants

Consecutive patients with a diagnosis of schizophrenia according to DSM-IV were enrolled from the Out Patient Department, Sarhad Hospital for Psychiatric Diseases, from 1st April 2016 to 30th November 2016. Patients were assessed by a consultant Psychiatrist and referred to a trained interviewer after taking initial consent. Patients were given detailed information about the study and the interviewer obtained subsequently written consent. Thirty patients refused to participate. Those who declined participation were demographically similar to the ones who agreed to participate.

2.3. Inclusion and exclusion criteria

Only those patients were enrolled in the study who had at least a 1-year history of schizophrenia. Patients with an organic brain disorder, intellectual disability or polysubstance abuse were excluded from the study

2.4. Assessment

The same interviewer assessed all the patients under the supervision of a consultant psychiatrist. Information was obtained directly from the patient and their immediate caregivers and, with patients' consent, from their hospital medical records.

Detailed demographic and clinical data were obtained including age, gender, age at onset of disease, duration of untreated psychosis, duration of illness, compliance with therapy, cannabis use, consanguinity, and family history of psychiatric illness. For consanguinity, we enquired about the relationship between parents and grandparents. We classed offspring of first cousins and second cousins as consanguineous and the rest as non-consanguineous. We decided to take this approach for the sake of simplicity. We are aware that there will be additional relatedness beyond the two generations, but we expect that background consanguinity will be similar in both groups.

For cannabis use, the following information was obtained: use before or after the onset of illness, duration of cannabis use in the lifetime, quantity, and status of current use. Current users were further classified as frequent, regular and infrequent. Frequent users were those who used cannabis more than five times in last two weeks, regular were those who used cannabis two to five times in last two weeks, and infrequent were those who used cannabis once in the last two weeks. Those who did not use cannabis in the last two weeks were labeled as not using it currently. Frequent and heavy users may still have cannabis in their bloodstream and also potentially may suffer from symptomatic cannabis withdrawal syndrome after cessation. Our choice of two weeks was primarily based on the expectation that recall within two weeks of use will be more reliable than a longer period. Use prior to two weeks will be counted as lifetime use.

Clinical evaluation and therapeutic response were established using Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and Clinical Global Impressions Scales-Severity (CGI-S) and Improvement (CGI-I) scale (Guy, 1976).

Patients were divided into two groups based on therapeutic response to different doses of antipsychotics; treatment responsive and treatment-resistant. We used the modified criteria of Liou et al. (2012).

Treatment responsive: Current treatment with antipsychotic medications in doses lower than 600 mg of chlorpromazine equivalent and current PANSS score less than three on following items: conceptual disorganization, suspiciousness, delusions, and hallucinations; CGI-S score of less than 4.

Treatment-resistant: Patients who did not respond to two six weeks' trials of APDs in doses less than 600 mg of chlorpromazine equivalent, with persistent conceptual disorganization, suspiciousness, delusions, and hallucinations (scored 3 or higher on PANSS). Currently on APDs at doses higher than 600 mg equivalent chlorpromazine or those who were prescribed clozapine. Response to previous medications was established from the medical record and by interviewing the patient and caregiver. The response was established by rating them on PANSS and CGI-S, and if they scored 3 or higher on conceptual disorganization, suspiciousness, delusions and hallucinations on PANSS and scored 4 or higher on CGI-S at higher doses, they were labeled as treatment resistant.

Patients compliance with medication was also checked, those who reportedly had compliance issues were labeled as Uncertain treatment response (UTR) and were excluded from further analysis. We assessed treatment adherence with the 4-item Morisky Medication Adherence Scale (Morisky et al., 1986). For a trial of oral medication to be counted we sought information from a family member about adherence. These family members were living with the patients and providing support to them. They confirmed that the medication is given to the patient under direct observation.

Duration of untreated psychosis was defined as the duration from the manifestation of first psychotic symptoms to first adequate APD treatment (Marshall et al., 2005).

2.5. Data analysis

Frequency, mean, standard deviation and percentages were used as appropriate for the purpose of description of the variables. For group comparisons ANOVA or Chi Square tests were used as appropriate. Logistic regression was used to examine the association between treatment response and study variables.

3. Results

A total of 294 patients were asked to participate, of whom 30 refused consent. Fifteen patients were excluded because they did not meet

Table 1
Demographic and clinical variables of patients.

Variables	Responsive *N*%	Resistant *N* (%)	*P*values
Participants	77 (33.48)	153 (66.52)	
Consanguinity			
Present	31 (65.96)	62 (66.67)	Chi square, $p = 1$
Absent	16 (34.04)	31 (33.33)	
Family history of neuropsychiatric illness			
Absent	40 (59.7)	91 (64.5)	Chi Square $p = 0.8$
Present	27 (40.3)	50 (35.5)	
	Mean ± SD	Mean ± SD	
Age - years	33.43 ± 10.39 (*N* 76)	34.62 ± 10.47 (*N* 148)	ANOVA $p = 0.4$
Age at onset - years	21.50 ± 5.85 (*N* 68)	21.27 ± 5.89 (*N* 140)	ANOVA $p = 0.8$
Duration of illness – years	11.85 ± 8.64 (*N* 68)	12.79 ± 8.39 (*N* 139)	ANOVA $p = 0.4$
Duration of untreated psychosis – months	17.83 ± 21.92 (*N* 44)	30.45 ± 38.91(*N* 85)	ANOVA $p = 0.04$
PANSS	47.92 ± 14.46 (*N* 77)	79.92 ± 26.08 (*N* 153)	ANOVA $p < 2e-16$
Positive score	12.07 ± 5.00(*N* 77)	22.79 ± 8.07 (*N* 153)	ANOVA $p < 2e-16$
Negative score	12.92 ± 5.22 (*N* 77)	20.59 ± 9.04 (*N* 153)	ANOVA $p = 5.49e-11$
General psychopathology	24.06 ± 6.76 (*N* 77)	36.86 ± 14.52 (*N* 153)	ANOVA $p = 6.07e-12$
Morinsky score *N* (%)			
0	65 (84.4%)	108(72.0%)	Chisq = 5.469, df = 4, $p = 0.24$
1	3 (3.9%)	9 (6.0)	
2	4 (5.2%)	9 (6.0%)	
3	1 (1.3%)	9 (6.0%)	
4	4 (5.2%)	15 (15.0%)	

the inclusion criteria. In 19 patients' treatment, response could not be established with confidence because of noncompliance. These patients were excluded from further analysis. Finally, 230 patients were included in the analysis. Of these participants77 were treatment responsive (TRP) and 153 were treatment resistant (TRS) according to study criteria (Table 1). There were 215 (93.57%) males and 15 (6.42%) females in the group. In TRP group 70 were male, and seven were female while in the TRS group 145 were male, and eight were female. In Table 1 we describe the sample and its characteristics.

The mean age at onset of illness (AAO) was 21.15 ± 5.76 ($n = 208$), data was missing for 22 individuals. In TRS and TRP, AAO was 21.50 ± 5.85 and 21.27 ± 5.89 respectively and not statistically different (ANOVA, *p*value 0.8)

Duration of untreated psychosis (DUP) was ascertained for 129 participants with data missing in 101 participants. The mean value of DUP was 25.87 ± 33.45 months for all participants. The DUP was statistically different for TRP and TRS (17.83 ± 21.92 and 30.45 ± 38.91, ANOVA, *p*value 0.04).

All the participants were evaluated on PANSS. The mean overall PANSS score for all participants was 69.94 ± 27.24, while mean positive, negative and general psychopathology score were 19.21 ± 8.74, 18.24 ± 8.68 and 32.83 ± 13.75 respectively.

We also obtained information about consanguinity. We had information for 140 participants' while for 90 individuals' information could not be ascertained. Consanguinity was present in 93 (40.04%) individuals overall. In all the groups' consanguinity was high which is typical in the Pakistani population. There was no statistical difference between the groups (Chi square p 1)

A family history of psychiatric illness was available for 208 individuals, and for 22 individuals' data was missing. Among the 208 individuals, family history was positive for psychiatric illness in 77 (33.48%). There was no statistical difference between treatment resistant and treatment responsive group (Chi Square p 0.86)

3.1. Antipsychotics use

Table 2 describes the current antipsychotic use in treatment resistant and treatment responsive groups. More people in treatment resistant group were on long acting depot antipsychotics and more people were receiving haloperidol in treatment resistant group. There was no difference in use of other antipsychotics between the groups.

For people who were not on clozapine we gathered information about use of antipsychotics in two previous trials. This is presented in Table 3. The treatment responsive people were seventy-seven in number so the total number of possible trials was one hundred and fifty-four. In treatment resistant group ninety-five people were not on clozapine and the total possible trials were one hundred and ninety. The number of trials of long acting depot antipsychotics, haloperidol, risperidone and olanzapine were significantly higher in the treatment resistant group.

In treatment responsive group 41 people were on single antipsychotic, 34 on two antipsychotics and 2 on three or more antipsychotics. In treatment resistant group twenty-one people who were on clozapine did not take any other antipsychotic. Thirty-two people had one other antipsychotic with clozapine and five people had two or more antipsychotics along with clozapine. Treatment resistant patients who were not taking clozapine were all on two or more antipsychotics. Thirty-three took two antipsychotics and sixty-two took three or more antipsychotics. Cannabis history was ascertained for 227 (98.69%) participants, and in 3 (1.31%) participants' data was unavailable (Table 4). Among those with available cannabis history, cannabis usage history was found in 95 (41.30%)individuals. As compared to TRP, TRS was enriched with positive cannabis history. The mean lifetime usage of cannabis in those with positive history was 8.86 ± 6.60 years. In TRP and TRS it was 6.36 ± 6.29 and 9.79 ± 6.18 respectively. The difference in the two groups was significant (p 0.03). There were 47 (20.23%) current users overall. The proportion of current users of cannabis was significantly higher in TRS (*p*-value 0.000194). The current users were further classified into frequent, regular and infrequent users. Overall there were 16 (6.95%) frequent, 18 (7.82%) regular, 13 (5.65%) infrequent users of cannabis. Further, we obtained information about first exposure to cannabis, whether it was before the onset of illness or after. The information was available for 73 individuals. Overall 52 started cannabis usage before the onset of illness and 21 started it afterward. The treatment resistance in non-cannabis users was 60% and in cannabis users it was 68% (Odds ratio 4.14 CI 1.50–14.27, p 0.002).

3.2. Logistic regression

We performed logistic regression to examine the association of AAO, DUP, consanguinity, 4-item Morisky Medication scale, family history of

Table 2
Current antipsychotics.

Medicine name	Resistant	Responsive	OR (CI)	*P*
Depot injection	85	25	2.6 (1.4–4.6)	**0.0005**
Haloperidol	46, 12.85 (± 3.47)*	4, 8.07 (± 2.43)*	7.8 (2.7–22.7)	**0.00007**
Risperidone	69, 6.91 (± 1.98)*	30, 5.19 (± 1.31)*	1.2 **(0.7–2.24)**	0.18
Olanzapine	81, 19.12 (± 4.21)*	43, 10.46 (± 4.43)*	0.88 (0.5–1.5)	0.33
Clozapine	58, 229 (± 91.71)*	0	N/A	
Quetiapine	3	1	1.5 (0.1–14.8)	0.35
Aripaprazole	4,16.87 (± 4.96)*	8, 22.5 (± 7.5)*	0.2 (0.06–0.7)	0.01
Trifluoperazine	12, 17.5 (± 4.03)*	3, 15 (0)*	2.09(0.5–7.6)	0.13
zuclopenthixol	4, 200 (0)*	1, 200 (0)*	2.04 (0.2–18.5)	0.26

* Mean dose and standard deviation.

Table 3
Count of antipsychotics used in two previous trials for people who are not on clozapine.

Medicine name	Resistant	Responsive	OR (CI)	*P*
Depot injection	69	24	3.0 (1.8–5.2)	**0.00001**
Haloperidol	31	3	9.8 (2.9–32.7)	**0.0001**
Risperidone	105	49	2.6 (1.6–4.1)	**0.000008**
Olanzapine	166	43	17.8 (10.2–31.0)	**2.2e−16**
Qutiapine	3	5	0.4 (0.07–2.5)	0.4
Aripaprazole	7	6	0.9 (0.2–3.4)	0.94
Trifluoperazine	11	3	3 (0.7–17.5)	0.09
zuclopenthixol	3	2	1.2 (0.1–14.7)	1

Table 4
Cannabis use history of patients.

Life time history of cannabis use	Treatment responsive *N* = 76	Treatment resistant *N* = 151	*P*value
Yes	26 (34.2)	69 (45.7)	Chi square $p = 0.09$
No	50 (65.8)	82 (54.3)	
Current users			
Total	5	42	Chi square *p*-value is 0.000194
Frequent users	2 (40)	14 (33.3)	
Regular users	2 (40)	16 (38.1)	
Infrequent users	1 (20)	12 (28.6)	
Usage started before or after onset of illness			
Before	14 (73.7)	38 (70.4)	Chi square $p = 1$
After	5 (26.3)	16 (29.6)	
Duration of use years	Mean (SD)	Mean (SD)	
Users	6.36 ± 6.29	9.79 ± 6.18	ANOVA 0.03

psychiatric illness, history of cannabis use, the lifetime duration of cannabis use, current cannabis use, quantity and use of cannabis before or after the onset of illness with treatment resistance (Table 5). The outcome variables in the model were treatment resistance and treatment response. Three variables, i.e. duration of cannabis use in the lifetime, current use and compliance with therapy (Morisky 4 item medication scale score), were significantly associated with treatment resistance with a *P*value of 0.031, 0.003 and 0.04 respectively (Table 5). With an odds ratio of 1.015429 (1.0014357- 1.033839) and *p*value of 0.059 duration of untreated psychosis had a significant trend for effect on treatment resistance. No significant association was found with age AAO, family history of psychiatric illness, consanguinity and use before or after the illness. Current use of cannabis was the only predictor that remained significant after Bonferroni correction.

4. Discussion

In this study, we examined the rate and predictors of treatment resistance specifically the past and current use of cannabis. The treatment compliance, current use and duration of use of cannabis were nominally associated with treatment resistance, and current use remained significant after Bonferroni correction. Despite decades of research, the causal link between cannabis and schizophrenia remains a sharply debated issue. Multiple studies have identified association, but the direction of causality is controversial (Burns, 2013). Many studies have examined the effect of cannabis use on the course of schizophrenia. In a two year follow up of first episode psychosis from Spain, use of cannabis after the onset of illness and lack of insight were the best predictors of relapse (Bergé et al., 2016). In another study, patients were followed up for ten years after their first admission with schizophrenia and found that cannabis use harmed their symptoms (Foti et al., 2010). In a Swedish study of 357 cases of schizophrenia for whom the historical data about use of cannabis was available, the use of cannabis increased the inpatient burden of care (Manrique-Garcia et al., 2014). In a cohort of 678 patients who were followed up for three years the persistent use of cannabis was associated with severe positive and negative symptoms and a higher number of relapses compared with

Table 5
Logistic regression results with treatment response and resistance as dependent variables.

Variables	*P*value	OR (95% CI)
Age at onset of illness (*N* = 208) (missing = 22)	0.800	0.99 (0.94–1.04)
Duration of untreated psychosis (*N* = 129) Missing = 101)	0.059	1.01 (1.00–1.03)
Compliance with therapy (Morinsky score) (*N* = 227) (missing = 3)	0.042	1.30 (1.02–1.71)
Consanguinity (*N* = 140) (missing = 90)	0.9	1.03 (0.48–2.15)
Family history of psychiatric illness (N 208) (missing = 22)	0.45	0.93 (0.78–1.11)
Life time Cannabis use history (*N* = 227) (missing = 3)	0.09	1.61 (0.91–2.89)
Life time duration of cannabis use (*N* = 204) (missing = 26)	0.031	1.06 (1.01–1.14)
Current use (*N* = 227) (missing = 3)	**0.003**	**2.04 (1.28 −3.24)***
Use before or after illness (*N* = 205) (missing = 25)	0.131	1.31 (0.92–1.86)

* Significant after Bonferroni correction.

non-users and those who discontinued usage (van der Meer et al., 2015). This effect is however not consistent across studies. In a study of first-episode psychosis, cannabis use did not have any effect on positive and negative symptoms during 24 months follow up (Hadden et al., 2016). Those studies have examined the course of illness in terms of the need for hospitalization and severity of symptoms. Compared with studies on the overall course of illness the effect of cannabis use on the effectiveness of antipsychotic medication is less well studied. The available literature suggests that cannabis use is associated with reduced effectiveness of antipsychotics (Knudsen and Vilmar, 1984; Swartz et al., 2008). Our findings lend further support to this hypothesis. This may be partly explained by the requirement of higher medication doses, dual morbidity of schizophrenia and the additional acute intoxicant effects following cannabis use in some patients. Furthermore, the pharmacokinetic and pharmacodynamics properties of cannabis may influence effective dopamine blockade.

Interestingly, one study has reported improved symptomology with clozapine in patients with cannabis associated schizophrenia as compared to other APDs (Tang et al., 2017). The better outcome with clozapine in those patients may be through clozapine effects on cannabinoid receptors (Sundram et al., 2005). Studies have extensively reported the role of the endocannabinoid system in schizophrenia and efforts are ongoing to develop new drugs acting on this system (Zamberletti et al., 2012).

There are distinct subgroups in treatment resistant schizophrenia; for some people it starts at onset while in others it starts later(Agid et al., 2011; Emsley et al., 2013, 2012; Howes et al., 2017; Kolakowska et al., 1985; Wiersma et al., 1998). Our threshold of inclusion was one year of illness. We might have missed some treatment resistance in people in the group who develop resistance later in the course of their illness.

We investigated the relationship between age at onset of illness and treatment response, as it has been reported that earlier age of onset is a predictor of severe psychopathology and treatment resistance (Lally et al., 2016; Meltzer et al., 1997). Furthermore, there is reportedly an increased risk of psychosis and schizophrenia with frequent, heavy use in younger persons with developing brains (Casadio et al., 2011; Gogtay et al., 2011). We did not find any association between age at onset and treatment resistance. Other studies have not found the relationship between age at onset and treatment resistance (Mena et al., 2018).

Apart from cannabis use, we investigated the effect of the duration of untreated psychosis on treatment response. Studies have reported that a longer duration of untreated psychosis leads to treatment resistance (Marshall et al., 2005; Murru and Carpiniello, 2018). We found a trend, albeit non-significant, towards poorer response and longer duration of untreated psychosis. We were not able to ascertain the duration of untreated psychosis in a significant proportion of the participants.

We also investigated the relationship between consanguinity and treatment response. We hypothesized that patients from highly consanguineous families would share a more substantial genetic burden and would have a severer form of the disease. We did not find a significant association between treatment response and consanguinity. A large percentage of marriages in KPK, Pakistan are consanguineous, and consanguinity was evenly distributed in both groups. Furthermore, we didn't find a significant association between a family history of psychiatric illness and treatment response. One interesting observation was the high proportion of consanguinity and family history of psychiatric illness overall in the cohort. However, its effect on treatment response was not observed.

As we wanted to study the link between cannabis use and treatment resistance, we selected our sample from a hospital where a higher proportion of patients have treatment resistance. The advantage was that we were able to examine the association as a high proportion of patients were treatment resistance. We, however, are not able to draw any results about the prevalence of treatment resistance in broader schizophrenia patients in Pakistan from this study. The rate of treatment resistance in people who are not currently using cannabis is also high (60%). Some studies have reported a lower rate compared with ours (Wimberley et al., 2016). We selected our sample from a tertiary care service where the prevalence of treatment resistance is high and that probably is the reason for a high level of resistance in non-cannabis users. In relative terms the cannabis users have a higher rate of resistance.

We did not use DSM criteria for cannabis use disorder (CUD). We gathered information about lifetime use and duration of use of cannabis. Our definition of current use of cannabis was based on a two weeks' window of use. We chose this to avoid recall bias but this may limit the opportunity to compare our data with studies that have used DSM cannabis use disorder (CUD) criteria. Because of limited resources available for this study we were not able to perform urine tests to rule in or out recent cannabis use. We however had collateral information from the family members who are the main source of support for patients in that culture.

Duration of untreated psychosis is one of the predictors of poor response to treatment. We were not able to ascertain data in majority of our patients about this variable. It is a weakness of the study.

The rater was not blind to cannabis use when assessing treatment resistance that creates the risk of bias.

A small number of female patients participated in the study. Fewer families in the province would like to take their female members in this hospital because of a strong stigma. These are the limitations of this study.

5. Conclusion

Frequent and regular use of cannabis was associated with treatment resistance in this study. Further studies are required on larger populations and different ethnicities to confirm these findings. If cannabis use contributes to treatment resistance, then it can be a target for treatment strategies to improve the outcome of schizophrenia.

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Supplementary materials

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