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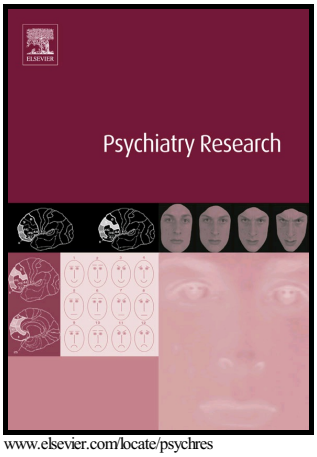

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Effect of continued cannabis use on medication adherence in the first two years following onset of psychosis

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Abstract

Uncertainty exists whether the use of non-prescription psychoactive substances following onset of a first episode of psychosis (FEP), in particular cannabis use, affects medication adherence. Data from FEP patients (N=233) obtained through prospective assessments measured medication adherence and pattern of cannabis and other substance use in the first two years following onset of psychosis. Multiple logistic regression analyses were employed to compare the different substance use groups with regard to risk of medication non-adherence, while controlling for confounders. The proportion of non-adherent patients was higher in those who continued using high-potency forms of cannabis (skunk-like) following the onset (83%) when compared to never regular users (51%), corresponding to an Odds Ratio (OR) of 5.26[95% Confidence Interval (CI) 1.91-15.68]. No significant increases in risk were present in those who used cannabis more sporadically or used milder forms of cannabis (hash-like). Other substances did not make an independent contribution in this model, including cigarette use ([OR 0.88, 95% CI 0.41-1.89]), alcohol use ([OR 0.66, 95% CI 0.27-1.64]) or regular use of other illicit drugs ([OR 1.03, 95% CI 0.34-3.15]) following the onset. These results suggest that continued use of high-potency cannabis following the onset of psychosis may adversely affect medication adherence.

Keywords: Cannabis, THC, first episode psychosis, epidemiology

1. Introduction

Despite the effectiveness of antipsychotic medication in preventing relapse following the first episode of psychosis (FEP) (Leucht et al., 2012), relapse is a common occurrence, often due to non-adherence to prescribed medication (Verdoux et al., 2000; Coldham et al., 2002; Üçok et al., 2006; Morken et al., 2008; Gearing et al., 2009; Hill et al., 2010; Lambert et al., 2010; Caseiro et al., 2012; Levy et al., 2012; Barbeito et al., 2013; Hui et al., 2013). Although the reported rates vary considerably across studies (Sendt et al., 2015), estimates from systematic reviews indicate that an average of 26% of patients with psychosis do not adhere to their

treatment plan (Nose et al., 2003). Particularly during the early stages of psychosis the rates of medication non-adherence are high (>50%) (Coldham et al., 2002; Schimmelmann et al., 2007; Lambert et al., 2010; Schoeler et al., 2016), which is consistent with the finding that young patients are more likely than older ones to be non-adherent (Coldham et al., 2002; Kampman et al., 2002). For instance, more than 60% of FEP patients had at least one or more gaps in their antipsychotic medication use in the first year following their first episode of psychosis (Mojtabai et al., 2002). This early stage is also considered the "critical period" that determines long-term outcome in psychosis (Birchwood et al., 1997) and during which antipsychotic medications, if taken regularly, appear to be more effective in improving outcome than in the later stages of the illness (Hogarty 1993). Therefore, better understanding of factors that adversely influence adherence to medication treatment in the early period following onset of psychosis is particularly important in order to develop interventions that may help improve medication and long-term outcome in psychosis.

However, there is uncertainty regarding the factors that characterise non-adherent patients with psychosis. Although experience of side effects and lack of insight seem intuitively to be the most important contributors to non-adherence, evidence does not always support this (Mueser et al., 1990; Coldham et al., 2002; Mutsatsa et al., 2003; Kamali et al., 2006; De Haan et al., 2007). Anecdotal evidence from clinical settings suggests that another potentially important factor affecting adherence to antipsychotic medications is drug use, particularly use of cannabis use. However, comorbid cannabis use has often not been considered in multifactorial prediction models (Mueser et al., 1990; Kampman et al., 2002; Drake et al., 2015), despite being the most commonly used drug of abuse prior to (Van Mastrigt et al., 2004) and following the onset (Lange et al., 2014) of psychosis. While some evidence regarding the association between cannabis use and medication adherence exist(Foglia et al., under review), current evidence remains inconclusive due to limitations of existing studies

such as underpowered samples (Verdoux et al., 2000; Miller et al., 2009; Schimmelmann et al., 2012), inclusion of patients that are at different stages of their illness (Rittmannsberger et al., 2004; Pogge et al., 2005; Novick et al., 2010; Jonsdottir et al., 2013) or cross-sectional study designs (Jonsdottir et al., 2013). In particular, lack of consideration of different patterns of cannabis use following onset of psychosis (Kampman et al., 2002; Perkins et al., 2006) limits the interpretability of current evidence, especially because cannabis is a pharmacologically complex plant whose effects are likely to depend on the type and dose of cannabis used, as well as pattern of its use (Di Forti et al., 2015; Schoeler et al., 2016; Schoeler et al., 2016). Furthermore, studies have often grouped cannabis users with users of other substances (Verdoux et al., 2000; Mutsatsa et al., 2003; Opolka et al., 2003; Kamali et al., 2006) which prevents conclusions being drawn about whether the effects may be attributed to a specific drug. For instance, users of illicit drugs may not take their antipsychotic medication so as not to blunt the pleasurable effects of the substance. Hence, it is important to examine whether medication non-adherence is generally associated with the use of any illicit drugs or is specifically associated with cannabis use. There is thus a need to distinguish between the different substances of use including cannabis, alcohol, cigarettes and other illicit drugs. Finally, it may be argued that worsening of psychotic symptoms (Schoeler et al., 2016) and cognitive function (Schoeler and Bhattacharyya 2013) as a result of cannabis use may interfere with the ability to regularly take the prescribed dose of medication. If this was the case, no link should exist between cannabis use and medication adherence in those whose illness course is not affected by the use of cannabis, which has not been examined previously.

In order to address limitations of existing evidence and to extend current evidence, this study has the following aims:

(1) To systematically evaluate the effect of different patterns of cannabis use following the onset of psychosis on the risk of non-adherence to prescribed antipsychotic medication

(2) To evaluate and control for the effects of patterns of use of other commonly used non-prescription psychoactive substances following onset of psychosis, including alcohol, cigarette and illicit drugs other than cannabis

(3) To control for important confounders including clinical and demographic characteristics

(4) To test whether an association between cannabis use and non-adherence is present in a subgroup of patients whose illness course is not affected by cannabis use (i.e. including only non-relapsing FEP patients)

2. Method

As part of a follow-up study aiming to investigate the role of cannabis within the first two years following onset, we recruited patients with first-episode non-organic [non-affective (ICD10 codes F20-F29) or affective (F30-F33)] psychosis (WHO 2004), aged 18-65 who were referred to local psychiatric services in South London. We have previously reported on methods for evaluation of subjects and data acquisition (Schoeler et al., 2016; Schoeler et al., 2016). This study was granted ethical approval by South London & Maudsley NHS foundation trust and Institute of Psychiatry Local Research Ethics Committee. All subjects included in the study gave written informed consent.

2.1 Measures

Cannabis use was assessed using a modified version of the Cannabis Experience Questionnaire (Schoeler et al., 2016), collecting data on premorbid cannabis use, as well as use over the first two years following onset of psychosis. Cannabis users were classified based on their pattern of use following onset, depending on continuity and type (hash-like vs.

skunk-like) (Di Forti et al., 2014; Schoeler et al., 2016) of cannabis use. Several covariates were included, based on previous literature (Verdoux et al., 2000; Coldham et al., 2002; Kampman et al., 2002; Mutsatsa et al., 2003; Kamali et al., 2006; Perkins et al., 2006; De Haan et al., 2007; Miller et al., 2009; Barbeito et al., 2013; Colizzi et al., 2015), including alcohol use, cigarette use, illicit drug use, gender, ethnicity, age of onset of illness, severity of illness at onset (measured as care intensity at onset, cf. below) and diagnosis.

2.2 Data analysis

Data analysis was performed using R (R Core Team 2015). The cannabis profile variable was coded as an ordered categorical variable (cf. *Table 2.*), with the never (regular) user group acting as the reference group. As the main outcome of interest, medication adherence within the first two years following onset was assessed using the Life Chart Schedule (WHO 1992; Susser et al., 2000). Similar to previous reports (Faridi et al., 2012), the variable was dichotomized (adherence vs. non-adherence), rating a patient as compliant if the prescribed medication was taken regularly for more than 66% of the time within the two years following the onset of illness (i.e. non-adherent for less than 34% of the time). Several covariates were included, including:

a) Alcohol use: the alcohol use variable was dichotomized, classifying subjects as alcohol users if they had a history of daily use for at least one month within the first two years following onset of illness
b) Other drug use: other drug use was defined as use of illicit drugs other than cannabis within the first two years following onset. This variable was coded as a categorical variable [2=regular use (6 times or more); 1=experimental use (less than 6 times); 0 (reference group)=no use]
c) Cigarette use: the variable assessing cigarette use in the first two years following onset was coded as a categorical variable [2=continued use (>12 months of regular

use); 1=intermittent use (>2 months of regular use); 0 (reference group) = no regular use];

d) Diagnosis [affective vs. non-affective psychosis] was assessed based on ICD-10 diagnosis using OPCRIT(McGuffin et al., 1991) criteria]

e) Ethnicity was recorded according to the classification proposed by the UK Office for National Statistics(ONS 2012) [0 (reference group)=White; 1=Asian; 2=African; 3=Mixed/multiple ethnic groups]

f) Age of onset of illness was included as a categorical variable [0 (reference group)=younger than 21 years old; 1=between 21 and 45 years old; 2=older than 45 years old], based on the age on the date of referral for a first episode psychosis

g) Care intensity was coded as a categorical variable, rating each subject's intensity of service use when presenting to the psychiatric services for a first episode psychosis [0=Required only community treatment without crisis intervention; 1=Required crisis intervention without hospital admission; 2= Required hospital admission]

First, we ran simple logistic regression models to examine the uncontrolled effect of each of the specified predictors of interest separately. Then we employed multiple regression models to test whether the categorical cannabis variable remained a significant predictor after controlling for the effects of those specified covariates. It may be argued that some patients may struggle to take antipsychotic medication as a result of being too unwell and having a relapsing course of illness, rather than necessarily being an effect of cannabis use. Although this is not easy to disentangle, we attempted to address this issue by investigating whether the association between cannabis use and risk of non-adherence was also present in those patients who did not have a relapsing course of illness. Relapse was defined as admission to a psychiatric inpatient unit owing to exacerbation of psychotic symptoms within two years

following first presentation to psychiatric services and receiving a diagnosis of psychosis (Addington et al., 2012; Olivares et al., 2013; Schoeler et al., 2016).

3. Results

3.1 Sample characteristics

Over the first two years following onset, 59.2% (n=138) of the patients were not adherent to their prescribed medication (cf. *Table 1.*). Compared to those who were adherent, the non-adherent group differed significantly in several variables, i.e. they were different in their cannabis use following onset (χ^2=17.52; p=0.002), more likely to be male (χ^2=5.36; p=0.02), and of different ethnic background (χ^2=9.66; p=0.02). The two groups (adherent vs. non-adherent) did not significantly differ with regard to other substance use including cigarettes (χ^2=2.36; p=0.31), alcohol (χ^2=0.14; p=0.71) and illicit drugs (χ^2=1.03; p=0.60). In the group classified as regular users of other illicit drugs following the onset (n=26, 11.2%), n=18 (69.2%) used cocaine, n=8 (30.8%) used opioids, n=8 (30.8%) used amphetamines, n=3 (11.5%), used hallucinogens, n=2 (7.7%) used poppers and n=1 (3.8%) used ketamine. 40.3% (n=94) have never used cannabis regularly in their life. A subset of patients (19.3%, n=45) used cannabis regularly prior to but did not report use following onset of psychosis. Cannabis use following onset was reported by n=94 (40.3%) patients (mean age of onset of use 17.3 years, 3.99 SD), including n=34 (14.6%) who used it intermittently and n=60 (25.8%) who used continuously (each month within the two years following onset). Most of the post-onset users had a history of regular cannabis use prior to onset (n=91, 96.8%) and used cannabis during the month preceding onset of illness [n=80, 93% (missing data for n=13)]

3.2 Cannabis use and risk of non-adherence

As shown in the simple logistic regression model in *Table 2.*, out of the five different cannabis use groups, only those classified as continued users of skunk-like cannabis were significantly more likely to be non-adherent with their prescribed medication when compared to never regular users [OR_{simple}=4.58; 95% CI 2.08-10.99, p<0.001]. The other cannabis use groups were not significantly different when compared to the never regular user group, including former (regular) cannabis users [OR_{simple}=0.84; 95% CI 0.41-1.71, p=0.63], intermittent cannabis users [OR_{simple}=1.55; 95% CI 0.70-3.52, p=0.29] or continued users of hash-type cannabis [OR_{simple}=1.60; 95% CI 0.37-8.15, p=0.54]. The magnitude of effect of continued use of skunk-like cannabis remained significant in the multiple logistic regression analysis [$OR_{multiple}$=5.26; 95% CI 1.91-15.68, p=0.002], in which the effect of all covariates specified in *Table 2.* was controlled for. In this controlled model, the effect of gender was no longer significant [$OR_{multiple}$ =1.7; 95% CI 0.91-3.21, p=0.10], while African [$OR_{multiple}$ =2.41; 95% CI 1.21-4.88, p=0.01] and Asian [$OR_{multiple}$ =4.53; 95% CI 1.22-19.78, p=0.03] ethnicity remained significant predictors for non-adherence. When the analysis was restricted to patients with a non-relapsing illness course (cf. *Table 3.*), cannabis remained a significant predictor for medication non-adherence in simple [OR_{simple}=4.11; 95% CI 1.42-13.84, p=0.01] and multiple logistic regression analyses [$OR_{multiple}$=4.61; 95% CI 1.13-22.23, p=0.04]

4. Discussion

More than half of our patients with a first episode psychosis did not comply with their antipsychotic medication within the first two years following onset, which is consistent with the high prevalence rates in FEP samples reported previously (Coldham et al., 2002; Schimmelmann et al., 2007; Lambert et al., 2010; Schoeler et al., 2016). Our results showed

that ongoing cannabis use following onset of psychosis was significantly associated with medication non-adherence even after controlling for potential confounders such as other illicit drug use and clinical and demographic characteristics. More specifically, when compared to never regular users, risk of non-adherence was greater in those who used skunk-like forms of cannabis continuously i.e. used at least monthly throughout the first 2 years following onset of psychosis. Risk was not significantly greater in those who used it more sporadically following onset or used milder forms of cannabis (hash-like), suggesting that potency and usage pattern of cannabis may determine the magnitude of effect of cannabis use on non-adherence. It is likely that the greater effect of skunk-like cannabis on medication adherence merely reflects the effect of exposure to the higher dose of delta-9-tetrahydrocannabinol present in skunk compared to hash-type cannabis and is consistent with previous evidence (Di Forti et al., 2014; Schoeler et al., 2016). This is in line with existing evidence, in which reductions in cannabis use were linked to improvements in adherence in FEP patients over the long-term (Barbeito et al., 2013). Our finding may also explain the absence of effect of cannabis use on medication adherence reported by studies that assessed cannabis use only at onset of psychosis (Coldham et al., 2002; De Haan et al., 2007). Hence, focusing on use patterns following onset may be a more useful indicator of adherence for clinicians during the early stages of the illness.

These results also suggest that this effect on non-adherence is a specific effect of cannabis use as no significant effect of other substances such as cigarette, alcohol or illicit drugs other than cannabis was observed on non-adherence. This is similar to results from other studies, in which use of illicit drugs (excluding cannabis) (Barbeito et al., 2013), alcohol (Verdoux et al., 2000; Coldham et al., 2002; Mutsatsa et al., 2003; Colizzi et al., 2015) or cigarette (Barbeito et al., 2013) was not predictive of adherence to medication. Only a few predictors other than cannabis use were significantly linked to medication non-adherence. For instance, a greater

risk of non-adherence was found in patients who were of African or Asian ethnicity, consistent with previous reports (Opolka et al., 2003). Male gender was significantly linked to medication non-adherence in univariate analysis but was no longer predictive in the controlled models, consistent with previous evidence reporting no gender effect (Mutsatsa et al., 2003; Kamali et al., 2006; Miller et al., 2009; Barbeito et al., 2013). Age of onset of psychosis, illness severity at onset (indexed care intensity at onset) and diagnosis were not associated with mediation non-adherence ,which is generally consistent with previous studies (Verdoux et al., 2000; Mutsatsa et al., 2003; De Haan et al., 2007; Barbeito et al., 2013), although inconsistencies exist (Kampman et al., 2002; García et al., 2016).

Recent evidence from a large study in first episode psychosis suggests that failure of treatment with prescribed antipsychotic medications may mediate the association between cannabis use and poor outcome characterized by relapse of psychosis leading to hospitalization (Patel R et al., 2016). The authors however could not establish whether treatment failure was a result of treatment resistance or non-adherence to antipsychotic medications. The present study extends these results suggesting that cannabis use may cause failure of treatment with antipsychotic medications by increasing the risk of non-adherence to treatment. Whether it also increases the risk of resistance to antipsychotic medications is yet to be tested. There are several potential mechanisms through which cannabis use may be increase the risk of medication non-adherence, though these are yet to be tested. For instance, cannabis use, particularly the use of high-potency forms of cannabis such as skunk, may increase the risk of non-adherence through its dose-dependent effects on memory as reported by experimental (Curran et al., 2002) and observational studies (Bolla et al., 2002; Schoeler and Bhattacharyya 2013; González-Pinto et al., 2016), resulting in cannabis-using patients forgetting to take prescribed medications. Prospective memory (i.e. the ability to remember to do things in the future such as taking medication) may be the memory domain most affected

by cannabis in those using the substance (Schoeler et al., 2016). Increased risk of non-adherence may also reflect the adverse effects of cannabis use on illness course via its effects on symptoms (González-Ortega et al., 2015; Schoeler et al., 2016) and risk of relapse (Schoeler et al., 2016) - adverse affects that have particularly been linked to the use of skunk-type forms of cannabis (Di Forti et al., 2015; Sideli et al., 2015; Schoeler et al., 2016). Experimental studies using delta-9-tetrahydorcannabinol, the main psychoactive ingredient in cannabis suggest that it can induce acute psychotic symptoms and alter memory processing in healthy volunteers (Bhattacharyya et al., 2009; Bhattacharyya et al., 2012; Bhattacharyya et al., 2012; Bhattacharyya et al., 2015) and affect them to a greater extent in patients with psychosis (D'Souza et al., 2005). Nevertheless, when restricting the analysis to a subsample of patients in whom illness course was not as adversely affected by cannabis use as evident from the fact that they did not experience relapses over the duration of follow-up, cannabis use remained a significant predictor for non-adherence. This may suggest that it is unlikely that non-adherence to antipsychotic medications is merely a result of a poor illness course rather than being a direct effect of cannabis use on adherence.

Some limitations have to be pointed out when interpreting these results. First, we assessed adherence to medication based on self-reports without taking into account drug-level measurements or pill counts. Nevertheless, self-reports are considered as a valid and appropriate method of measuring adherence especially when validated with serum concentration of medication (Jónsdóttir et al., 2010). While self-reports are likely to overestimate adherence, this is unlikely to have been systematically different in any of the cannabis use groups compared to others. Similarly, cannabis use was assessed based on self-reports, but these measures provide generally reliable estimates as observed when compared with biological measures (Di Forti et al., 2012), which has been done in this study. Further investigations on this topic should therefore add biological measures of cannabis use and

medication adherence obtained from commonly employed tests such as hair analyses or blood tests. Although it may be argued that we did not control for the type of medication that was prescribed following onset, this has previously not been linked to risk of medication non-adherence (Miller et al., 2009). Finally, we did not further evaluate mechanisms of action, e.g. whether level of insight into illness or response to antipsychotic medication played a role in the association between cannabis use and risk of non-adherence. Future studies should therefore explore the different pathways that may help explain the relationship we found in this study. It is worth noting that these results do not allow us to disentangle the possibilities that the effect of cannabis use on medication adherence as observed here may have been a result of its effect on symptoms and clinical presentation or an independent effect on compliance with antipsychotic medications or indeed both. Future studies may attempt to disentangle these possibilities. In this context it should also be pointed out that we did not further investigate whether the effects of cannabis use on outcome were mediated by its effect on medication adherence, which may be investigated in future using appropriately powered samples. Finally, it should be noted that we included a selective subset of inner city FEP patients. Hence, future studies need to replicate these results in patients from different geographical areas as well in patients at a later stage of their illness to confirm whether the results reported here also apply to other clinical settings and to those with a more chronic course of illness.

To summarise, continued use of high-potency cannabis is associated with a significantly greater risk of poor-adherence to antipsychotic medications in FEP patients. As cannabis use is a potentially preventable risk factor, interventions aimed at improving medication adherence in FEP should specifically target cannabis use, as reduction in cannabis use may lead to a more favourable illness course (Barbeito et al., 2013) and reduced cost of care (Offord et al., 2013) in FEP.

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Table 1. Sample characteristics

N		233
Gender	Female	92 (39.5%)
N (%)	Male	141 (60.5%)
Ethnicity	White	79 (33.9%)
	Asian	15 (6.4%)
	African	126 (54.1%)
	Mixed/Other	13 (5.6%)
Onset characteristics		
Mean age at onset (SD)		28.38 (8.47)
Diagnosis	Affective	42 (18%)
N (%)	Non-affective	191 (82%)
Onset care intensity	Community treatment	36 (15.5%)
	Crisis intervention	17 (7.3%)
	Hospitalisation	180 (77.3%)
History of (regular)	No	97 (41.6%)
cannabis use	Yes	136 (58.4%)
2-year follow up characteristics		
Course type	FEP only	143 (61.4%)
	Episodic	90 (38.6%)
Medication	Compliant	95 (40.8%)
adherence	Non-compliant	138 (59.2%)
Cigarette use	No use	99 (42.5%)
	Intermittent use	18 (7.7%)
	Continued use	116 (49.8%)
Alcohol use	No use	201 (86.3%)
	Continued use	32 (13.7%)
Cannabis use	Never	94 (40.3%)
	Former	45 (19.3%)
	Intermittent	34 (14.6%)
	Continued (Hash-type)	8 (3.4%)
	Continued (Skunk-type)	52 (22.3%)
Other illicit drug use	No use	193 (82.8%)
	Experimental	14 (6%)
	Regular use	26 (11.2%)

Table 2. Predictors for risk of medication non-adherence: Logistic regression models (N=233)

	Distribution			**Simple**			**Multiple**[b]		
	Adherent (n=95)	Non-adherent (n=138)	*p*[a]	*OR*	*95% CI*	*p*	*OR*	*95% CI*	*p*
Cannabis use			**0.002**						
Never	46 (48.9%)	48 (51.1%)		*1*			*1*		
Former	24 (53.3%)	21 (46.7%)		0.84	0.41 - 1.71	0.63	1.13	0.47 - 2.73	0.79
Intermittent	13 (38.2%)	21 (61.8%)		1.55	0.70 - 3.52	0.29	2.03	0.76 - 5.68	0.16
Continued (Hash-type)	3 (37.5%)	5 (62.5%)		1.60	0.37 - 8.15	0.54	1.50	0.28 - 9.22	0.64
Continued (Skunk-type)	9 (17.3%)	43 (82.7%)		4.58	2.08 - 10.99	**<0.001**	5.26	1.91 - 15.68	**0.002**
Other illicit drug use			0.60						
No use	81 (42%)	112 (58%)		*1*			*1*		
Experimental	4 (28.6%)	10 (71.4%)		1.81	0.58 -	0.33	1.97	0.48 -	0.36

					6.78			9.27	
Regular use	10 (38.5%)	16 (61.5%)		1.16	0.51 - 2.76	0.73	1.03	0.34 - 3.15	0.96
Cigarette use			0.31						
No use	46 (46.5%)	53 (53.5%)		*1*			*1*		
Intermittent use	7 (38.9%)	11 (61.1%)		1.36	0.50 - 3.98	0.55	0.88	0.26 - 3.06	0.84
Continued use	42 (36.2%)	74 (63.8%)		1.53	0.89 - 2.65	0.13	0.88	0.41 - 1.89	0.74
Alcohol use			0.71						
No use	81 (40.3%)	120 (59.7%)		*1*			*1*		
Regular use	14 (43.8%)	18 (56.2%)		0.87	0.41 - 1.87	0.71	0.66	0.27 - 1.64	0.37
Gender			**0.02**						
Female	46 (50%)	46 (50%)		*1*			*1*		
Male	49 (34.8%)	92 (65.2%)		1.88	1.10 - 3.22	**0.02**	1.7	0.91 - 3.21	0.10
Ethnicity			**0.02**						
White	43 (54.4%)	36 (45.6%)		*1*			*1*		
Asian	4 (26.7%)	11 (73.3%)		3.28	1.03 - 12.67	0.06	4.53	1.22 - 19.78	**0.03**
African	44 (34.9%)	82 (65.1%)		2.23	1.26 - 3.98	**0.01**	2.41	1.21 - 4.88	**0.01**
Mixed	4 (30.8%)	9 (69.2%)		2.69	0.80 - 10.59	0.12	2.72	0.69 - 12.26	0.16
Age of onset			0.92						
Younger than 21	16 (38.1%)	26 (61.9%)		*1*			*1*		
Between 21 and 45	73 (41.2%)	104 (58.8%)		0.88	0.43 - 1.74	0.71	1.33	0.60 - 2.96	0.48
Older than 45	6 (42.9%)	8 (57.1%)		0.82	0.24 - 2.90	0.75	1.75	0.45 - 7.16	0.42
Onset care intensity			0.21						
Community treatment	19 (52.8%)	17 (47.2%)		*1*			*1*		
Crisis intervention	8 (47.1%)	9 (52.9%)		1.26	0.39 - 4.07	0.70	1.81	0.47 - 7.16	0.39
Hospitalisation	68 (37.8%)	112 (62.2%)		1.84	0.90 - 3.82	0.10	2.08	0.93 - 4.77	0.08
Diagnosis			0.09						
Affective	22 (52.4%)	20 (47.6%)		*1*			*1*		
Non-affective	73 (38.2%)	118 (61.8%)		1.78	0.91 - 3.51	0.09	2.07	0.96 - 4.54	0.07

[a] *p*-values estimated from chi-square tests
[b] Multiple logistic regression analysis including all covariates listed in this table

Table 3. Sensitivity analysis: Cannabis use and risk of medication non-adherence in non-relapsing FEP patients[a]

	Simple			**Multiple[b]**		
	OR	*95% CI*	*p*	*OR*	*95% CI*	*p*
Cannabis use						
Never	1			1		
Former	0.64	0.26 - 1.52	0.32	0.6	0.19 - 1.82	0.37
Intermittent	1.71	0.64 - 4.75	0.29	2.62	0.73 - 10.19	0.15
Continued (Hash-type)	0.43	0.02 - 3.55	0.47	0.35	0.01 - 3.93	0.43
Continued (Skunk-type)	4.11	1.42 - 13.84	**0.01**	4.61	1.13 - 22.23	**0.04**

[a] Includes only patients with good clinical outcome (non-relapsing within the first two years following onset, n=143)
[b] Multiple logistic regression analysis including all covariates listed in this *Table 2.*

Highlights

- The study examined the effect of cannabis use on risk of medication non-adherence in psychosis
- Use of high-potency forms of cannabis following the onset predicted medication non-adherence
- The effect remained significant when potential confounders were considered
- More sporadic use of cannabis was not linked to medication non-adherence
- Similarly, the use of milder forms of cannabis (hash-like) was not associated with non-adherence