Psychological Medicine (2014), **44**, 117–126. © Cambridge University Press 2013
doi:10.1017/S0033291713000433

ORIGINAL ARTICLE

Change in cannabis use, clinical symptoms and social functioning among patients with first-episode psychosis: a 5-year follow-up study of patients in the OPUS trial

L. Clausen, C. R. Hjorthøj, A. Thorup, P. Jeppesen, L. Petersen, M. Bertelsen and M. Nordentoft*

Psychiatric Center Copenhagen, Copenhagen University, Faculty of Health Sciences, Copenhagen, Denmark

Background. Several studies indicate that cannabis use among patients with psychotic disorders is associated with worse outcome, but only a few studies have controlled for baseline condition and medication.

Method. At 5-year follow-up, interviews were carried out with 314 first-episode psychosis patients included in the OPUS trial. The patients included were in the age range of 18 to 45 years old and 59% were male. Cannabis use was extracted from the Schedule for Clinical Assessment in Neuropsychiatry. At follow-up, the patients were divided into different groups according to the variable cannabis use: abstainers, stoppers, starters and continuers. Psychotic, negative and disorganized dimensions (ranging from zero to five) were calculated for each of the four groups based on the Schedule for the Assessment of Positive and Negative Symptoms in Schizophrenia.

Results. Cannabis users were younger (24.6 years *v.* 27.4 years, $p<0.001$) and had a lower level of education. At the 5-year follow-up, users of cannabis had higher scores on the psychotic dimension [difference 0.97, 95% confidence interval (CI) 0.41–1.53, $p=0.001$] and lower levels of the Global Assessment of Functioning (difference 8.26, 95% CI 2.13–14.39, $p=0.01$). Those who stopped using cannabis between entry and 5-year follow-up had a significantly lower level of psychotic symptoms at 5-year follow-up even after controlling for baseline level of psychotic symptoms and for insufficient antipsychotic medication (adjusted difference in psychotic dimension –1.04, 95% CI –1.77 to –0.31, $p=0.006$).

Conclusions. Continuous cannabis use was associated with higher levels of psychotic symptoms after 5 years, and this association was only partly explained by insufficient antipsychotic medication.

Received 6 July 2012; Revised 7 February 2013; Accepted 7 February 2013; First published online 16 April 2013

Key words: Cannabis, cohort, follow-up, medication, psychosis.

Introduction

Cannabis is the most frequently used illegal drug, and cannabis-related admissions to psychiatric hospital increased by approximately 300% during the last decade (Sundhedsstyrelsen, 2012).

Previous studies indicate that frequent cannabis use is associated with more psychotic relapses, more hospitalizations, worsening of psychotic symptoms and reduced compliance to treatment (Archie *et al.* 2007; Petersen *et al.* 2007; Miller *et al.* 2009; Faridi *et al.* 2012; Schimmelmann *et al.* 2012; van Dijk *et al.* 2012).

Especially reduced adherence to medical treatment seems to represent a problem, since it has been shown that medical treatment can reduce psychotic symptoms in first-episode psychotic patients despite continued cannabis exposure (Faridi *et al.* 2012). Moreover, it is well documented that early adolescent cannabis exposure is related to earlier onset of psychosis (Large *et al.* 2011; Zammit *et al.* 2011) and psychosis-like symptoms (Compton *et al.* 2009; Anglin *et al.* 2012; Dragt *et al.* 2012; van Dijk *et al.* 2012), especially if cannabis use starts before the age of 14 years (Schimmelmann *et al.* 2011). Psychosis is also found to be correlated with the frequency of cannabis use (Moore *et al.* 2007). This finding has been confirmed in a large study of siblings, which reduces the likelihood that unmeasured confounding explains the findings (McGrath *et al.* 2010). There is some support for these findings in animal studies as well (Rubino *et al.* 2012; Zamberletti *et al.* 2012).

In a review from 2008 regarding cannabis use in psychotic patients, it was concluded that the statistical power in studies within this area is limited, and that future research should have a longitudinal design, with repeated measures of psychopathology, use of

* Address for correspondence: Dr M. Nordentoft, Psychiatric Center Copenhagen, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark.
(Email: mn@dadlnet.dk)

cannabis, alcohol and other drugs, as well as baseline measures of function, illness severity and other characteristics that are known to be associated with poorer outcome in schizophrenia (Zammit *et al.* 2008). Hitherto, these points have only been addressed in rather small studies (Faridi *et al.* 2012; Schimmelmann *et al.* 2012; van Dijk *et al.* 2012).

Aim

The aim was to analyse the association between the pattern of cannabis abuse and a range of clinically important outcome measures among the patients with first-episode schizophrenia spectrum disorders who were included in the Danish OPUS trial (Petersen *et al.* 2005; Bertelsen *et al.* 2008).

We hypothesized that cannabis use would be associated with higher levels of such clinical symptoms as psychotic, disorganized and negative symptoms. We also hypothesized that the number of days spent in a psychiatric ward and days living in supported psychiatric housing would be increased by cannabis use, and that level of function would be decreased. Patients with substance abuse have been reported to be more likely not to adhere to antipsychotic medication (Kamali *et al.* 2006; Quach *et al.* 2009), and this can independently affect the above-mentioned outcome measures. We hypothesized treatment compliance to be deficient in patients with cannabis use and that this could explain differences in clinical outcome to some degree.

We wanted to analyse how clinical and social outcome measures were affected in patients with different patterns of cannabis use. We wanted especially to investigate four different groups of patients: abstainers, stoppers, starters and continuers, categorized according to whether they had no use of cannabis or stopped, started or continued cannabis use during the 5-year period.

Method

All patients participated in the OPUS trial, a randomized clinical trial comparing specialized assertive early intervention treatment with standard treatment in first-episode psychosis. In this paper, we analyse all the patients as one cohort. Since the aim of this paper is not to investigate the effect of standard treatment *versus* specialized assertive early intervention services (OPUS), it is not relevant to describe the two types of treatment in detail (Petersen *et al.* 2005; Thorup *et al.* 2005).

Patients aged between 18 and 45 years were included if they met the criteria for International Classification of Diseases, 10th Revision (ICD-10) diagnoses within the schizophrenia spectrum (F2). All patients had to be able to speak and understand Danish; none of the patients had been treated with antipsychotic medication for more than 12 weeks; and the psychiatric symptoms were not due to any organic condition. Use of psychoactive drugs did not cause exclusion as long as the psychotic condition was not solely explained by poisoning or a withdrawal state.

As described in previous papers (Bertelsen *et al.* 2008; Nordentoft *et al.* 2010), 578 patients were included from January 1998 until December 2000. Of these, 314 participated in the 5-year follow-up, 17 had died, one disappeared, 10 moved out of the country and 236 declined to participate or could not be traced.

Baseline use of cannabis was not associated with not participating in follow-up interviews. Among those who used cannabis at baseline, 52% participated in the 5-year follow-up *versus* 55% of those who had used no cannabis during the last year or had used it less than monthly ($p=0.4$).

Assessment and data collection

All patients were interviewed and assessed by trained assessors who were blind to treatment allocation at entry and after 5 years.

As part of a comprehensive interview, several instruments were used to collect data. The variables listed below were derived from data obtained from interviews, register-based information and medical records.

Use of cannabis

Use of cannabis was assessed using Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interviews, versions 2.0 and 2.1 (since 1999) (Wing *et al.* 1990). Cannabis use was extracted from the SCAN interview, chapter 12, dichotomizing 'use of cannabis previous year' (item 12.007) into 'use' defined as any use in the previous year. Based on information about cannabis use (any cannabis use *versus* no cannabis use) during the previous year (chapter 12, item 12.007 in the SCAN interview), at entry, and at the 5-year follow-up interview, patients were divided into four groups: (1) abstainers – no use of cannabis at baseline and at 5-year follow-up; (2) stoppers – stopped cannabis use within the last 5 years; (3) starters – started cannabis use within the last 5 years; and (4) continuers – continued use of cannabis throughout the 5 years.

Sociodemographic information

Sociodemographic information on education, civil status, children and accommodation was extracted from interviews.

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

Psychopathological symptoms

Psychopathological symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). These were summarized in three psychopathological dimensions (Arndt *et al.* 1995): psychotic dimension (mean global scores for hallucinations and delusions); disorganized dimension (mean global scores for bizarre behaviour, formal thought disorder, and the single item 'inappropriate affect'); the negative dimension (mean global scores for affective flattening, alogia, avolition and anhedonia). These three dimensions were used as measures of psychopathology, ranging from zero to five. Inter-rater reliability between the assessors was measured with intra-class correlation coefficients, 0.90 for negative symptoms and 0.92 for psychotic symptoms, which reflect very good agreement (Bertelsen *et al.* 2008).

Insufficient medication

Patients were divided into two groups based on information about prescriptions for antipsychotic medication and compliance. Patients were classified as insufficiently medicated if they had not started or had discontinued medication or took medication irregularly, or if they had psychotic symptoms at a mild level or worse and no prescription for antipsychotic medication. Patients who had no psychotic symptoms, and patients who reported taking medication regularly as prescribed, were classified as sufficiently medicated. Blind researchers made the global measure of medication compliance based on structured interviews with the patients, information from the primary case manager and psychiatrist, and through systematic examination of the case notes and prescription cards.

Remission of symptoms

Patients were classified as being in remission with regard to negative symptoms, if none of the global scores in SANS exceeded the mild level of severity. Regarding psychotic symptoms, patients were considered remitted if the global scores for both hallucinations and delusions did not exceed the mild level of severity (Andreasen *et al.* 2005).

Course of illness

Course of illness was assessed with the Life Chart Schedule. Patients who had less than 6 months without psychotic symptoms within the last 2 years were classified as having continuous psychosis. Patients were classified with 'episodic psychotic illness' if they had psychotic symptoms during the last 2 years but did not fulfil the criteria for continuous psychosis. Patients were classified as 'not psychotic' if they had no psychotic symptoms during the last 2 years (WHO, 1992).

Duration of untreated psychosis

Duration of untreated psychosis was counted in weeks, and was assessed at entry to the study using the Interview for Retrospective Assessment of Onset of Schizophrenia (Häfner *et al.* 1992).

Pre-morbid functioning

Pre-morbid functioning was assessed retrospectively by the Premorbid Adjustment Scale (PAS) (Cannon-Spoor *et al.* 1982), based on an interview with the patient. The PAS conceptualizes good pre-morbid adjustment as the achievement of certain age-appropriate developmental goals. Several reports of factor analyses confirm that the PAS covers two discrete areas of functioning: academic ('scholastic performance', 'adaptation to school') and social ('sociability and withdrawal', 'peer relations', and 'socio-sexual aspects') (Larsen *et al.* 2004; Jeppesen *et al.* 2008). Both factors are multiplied by 10, thus ranging from 0 to 10; 0 being optimal function, 10 being worst possible.

Symptoms and level of social functioning

The Global Assessment of Functioning (GAF) is a global measure of symptoms and level of social functioning. We used the split version of the GAF, divided into two scales: symptoms and level of social functioning. The scale ranges from 1 to 100, where 100 is the best and 1 is the worst (Pedersen *et al.* 2007).

Pre-morbid intelligence

The Danish Adult Reading Test (DART) is a Danish version of the National Reading Test (Nelson & Willison, 1982; Russell *et al.* 2000). The scores on the test are indicators of pre-morbid intelligence. This measure was applied at the 5-year follow-up interview.

Dosage of antipsychotic medication

Dosage of antipsychotic medication was measured by haloperidol equivalents.

Number of family and friends

The number of family and friends is based on the social network scale – the number of friends and family members with whom the patient has been in contact during the last month (Dunn *et al.* 1990).

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

Table 1. *Clinical and social factors among 578 patients with first-episode psychosis with at least monthly cannabis use compared with no use or less than monthly use*[a]

	All patients (n=578)	Cannabis use last year (n=191)	No cannabis use last year (n=387)	p
Sex, male, *n* (%)	343 (59.3)	148 (77.4)	195 (50.4)	<0.0001
Mean age, years (S.D.)	26.5 (6.3)	24.6 (5.7)	27.4 (6.3)	<0.0001
Completed high school, *n* (%)[b]	191 (33.5)	45 (23.6)	146 (38.5)	<0.0001
Completed vocational education, *n* (%)[b]	153 (26.8)	32 (16.8)	131 (31.8)	<0.0001
Mean DART (S.D.)[c]	31.20 (10.19)	32.06 (9.74)	29.40 (10.92)	0.04
Not married, *n* (%)	541 (94.6)	185 (96.9)	356 (93.4)	0.09
Living with children, *n* (%)	44 (7.7)	8 (4.2)	36 (4.5)	0.2
Lived with both parents until age 16 years, *n* (%)	364 (64.0)	105 (55.0)	259 (68.5)	0.002
Interview with family member, *n* (%)	245 (44.8)	83 (45.1)	162 (44.6)	0.9
Mean no. of family and friends (S.D.)	7.6 (5.5)	8.6 (5.3)	7.1 (5.5)	0.02
Mean pre-morbid adjustment, social functioning (x10) (S.D.)	3.0 (2.0)	2.6 (1.8)	3.2 (2.2)	0.001
Mean pre-morbid adjustment, academic functioning (x10) (S.D.)	4.2 (2.0)	4.6 (1.8)	3.8 (2.0)	<0.0001
Mean age at onset, years (S.D.)	24.4 (6.3)	22.8 (5.2)	25.2 (6.6)	<0.0001
Median duration of untreated psychosis, weeks[d]	52	42	53	0.4[e]
Mean GAF symptoms (S.D.)	33.3 (10.6)	33.5 (11.0)	33.2 (10.4)	0.7
Mean GAF function (S.D.)	40.9 (13.2)	40.6 (11.9)	41.1 (13.9)	0.3
Mean psychotic dimension (S.D.)	2.7 (1.5)	2.7 (1.5)	2.7 (1.4)	0.8
Mean disorganized dimension (S.D.)	1.0 (0.9)	1.1 (0.9)	1.0 (1.0)	0.2
Mean negative dimension (S.D.)	2.2 (1.2)	2.2 (1.0)	2.2 (1.2)	0.5

S.D., Standard deviation; DART, Danish Adult Reading Test; GAF, Global Assessment of Functioning.

[a] Almost all patients were able to complete the whole interview, but there are minor differences in the number for whom information is available.

[b] The DART was used only at the 5-year follow-up. Therefore, results of this test are available only for the patients who participated in the 5-year follow-up.

[c] Difference in the proportion of who completed high school and vocational education was significant even after adjusting for age.

[d] Patients with schizotypal disorder were excluded from this analysis.

[e] Mann–Whitney *U* test.

Hospitalizations and days in supported psychiatric housing

Register-based information about hospitalizations and days in supported psychiatric housing facilities was extracted from Danish national longitudinal registers (Pedersen *et al.* 2006; Mors *et al.* 2011; Nordentoft *et al.* 2012).

Statistical analysis

SPSS statistics version 19 (IBM, USA) was used for the statistical analyses. To analyse qualitative data, χ^2 tests were used; for the analyses of normally distributed data, two-tailed *t* tests were applied. The Mann–Whitney test was used to analyse duration of untreated psychosis, due to its skewed distribution. Logistic and linear regression analyses were used to evaluate whether differences in age could explain baseline differences in level of education. Univariate general linear model analyses were used to analyse the differences in 5-year outcome between the four groups with different patterns of use. These analyses were adjusted for baseline values of the scales, for sufficient antipsychotic medication and for age. Values of p lower than 0.05 were considered significant.

Results

Baseline data

Baseline data are shown in Table 1. Patients with cannabis use were predominantly males. They were 2.8 [95% confidence interval (CI) 1.8–34.9] years younger than the non-users, and they had an earlier age of onset of psychosis of 2.4 (95% CI 1.3–3.5) years. Fewer had lived in a family with both parents until 16 years of age (55.0% *v.* 68.5%, p=0.002).

The educational level for the cannabis users was significantly lower than among those with no use of cannabis. The proportion that completed high school

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

Table 2. *Clinical status, service use, and compliance with medication among first-episode patients with at least monthly cannabis use compared with no use or less than monthly use at 5-year follow-up*

	All patients who participated in 5-year follow-up (n=314)	Cannabis use during year before 5-year follow-up (n=37)	No cannabis use during year before 5-year follow-up (n=277)	χ^2/t test: p
Mean psychotic dimension (S.D.)	1.38 (1.61)	2.22 (1.70)	1.25 (1.56)	0.001
Mean disorganized dimension (S.D.)	0.43 (0.76)	0.54 (0.63)	0.42 (0.77	0.3
Mean negative dimension (S.D.)	1.74 (1.37)	1.99 (2.00)	1.70 (1.39)	0.2
Continuous course of illness, n (%)	143 (45.5)	24 (64.9)	119 (43.0)	0.04
Remission of psychotic symptoms, n (%)	172 (55.5)	11 (29.7)	161 (55.5)	0.001
Remission of negative symptoms, n (%)	129 (41.6)	9 (24.3)	120 (44.0)	0.02
Mean GAF, symptoms (S.D.)	53.59 (17.04)	48.2 (16.4)	54.4 (17.1)	0.03
Mean GAF, function (S.D.)	54.70 (17.73)	47.6 (17.4)	55.8 (17.6)	0.01
Mean haloperidol equivalents (S.D.)	1.72 (2.5)	2.1 (2.5)	1.66 (2.6)	0.4
Compliance with medication[a], n (%)	261 (84.2)	26 (70.3)	235 (86.1)	0.01
Register-based information				
Mean number of days in supported psychiatric housing facilities during first 5 years[b] (S.D.)	113.1 (350.3)	230.4 (459.6)	112.2 (318.7)	0.06
Mean number of days in supported psychiatric housing facilities, fifth year[b] (S.D.)	31.2 (98.3)	46.0 (119.3)	28.2 (95.9)	0.3
Mean number of psychiatric bed days during first 5 years[b] (S.D.)	193.4 (282.2)	199.7 (287.6)	189.9 (284.1)	0.8
Mean number of psychiatric bed days, fifth year[b] (S.D.)	22.0 (63.4)	29.5 (63.0)	21.5 (63.8)	0.5

S.D., Standard deviation; GAF, Global Assessment of Functioning.

[a] Compliant with antipsychotic medication or no prescription and not psychotic.

[b] Use of bed days in psychiatric departments and use of days in supported psychiatric housing facilities extracted from complete longitudinal Danish registers. The remaining variables in this table were extracted from 5-year follow-up interviews with minor differences in the number of patients for whom the information was available.

was 23.6% *v.* 38.5% (odds ratio 0.49, 95% CI 0.33–0.73, p<0.0001), and the proportion that completed vocational education was 16.8% *v.* 31.8% (odds ratio 0.43, 95% CI 0.28–0.67, p<0.0001). Age differences between the two groups did not explain the difference in the proportion completing high school or completing a vocational education. Cannabis users had 29.40 correct answers in the DART compared with 32.06 among those with no use of cannabis (mean difference 2.66, 95% CI. 0.14–5.18, p=0.04). In the PAS, the cannabis users had a significantly worse score on the academic dimension (mean difference 0.93, 95% CI 0.54–1.32, p<0.0001) and a significantly better score on the social dimension (mean difference 0.59, 95% CI 0.1–0.98, p=0.003). They also had significantly more contact with family and friends during the month before the baseline interview (8.6 *v.* 7.1, p=0.02).

At entry, there was no significant difference in the psychotic, negative or disorganized symptoms between the two groups.

Follow-up at 5 years

The 5-year follow-up data are presented in Table 2. Compared with the patients with no use of cannabis, patients with cannabis use had a significantly higher level of psychotic symptoms (difference in psychotic dimension 0.97, 95% CI 0.41–1.53, p=0.001), and a smaller proportion had remission of psychotic symptoms (29.7% *v.* 55.5%, p=0.001) and negative symptoms (24.3% *v.* 44.0%, p=0.02). The cannabis users were more likely to have a continuous course of illness (64.9% *v.* 43.0%, p=0.04), and they had a higher level of symptoms and lower level of social functioning; thus, the difference in the GAF symptom dimension was 6.21 (95% CI 0.29–12.14, p=0.04) and in the GAF social dimension 8.26 (95% CI 2.13–14.39, p<0.01). A significantly lower proportion was classified as receiving sufficient antipsychotic medication (70.3% *v.* 86.1%, p=0.01). In order to investigate possible age differences between cannabis users and non-users, all significant

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

differences were analysed in logistic and linear regression models with age as a covariate. This did not change the results substantially.

In Table 3, the outcome measures are shown for the patient group. The patients are divided into four groups ('abstainers', 'stoppers', 'starters' and 'continuers') based on the pattern of development of cannabis use. The level of psychotic symptoms varied according to pattern of use ($p<0.01$), and so did treatment with antipsychotic medication ($p=0.03$). Neither the levels of disorganized symptoms nor the levels of negative symptoms were affected by patterns of cannabis use. Fig. 1 presents the clinical and social outcome for the four groups.

Differences in clinical outcome for 'abstainers', 'stoppers' and 'starters' compared with 'continuers' are presented in Table 4. Results of analyses with baseline value of the scores included as covariates, and analyses also adjusted for insufficient treatment with antipsychotic medication are presented. There were significantly lower scores on the psychotic dimension for 'abstainers' and 'stoppers' compared with 'continuers' ($p=0.006$). These findings were still significant when the analyses were adjusted for insufficient antipsychotic medication. Further adjustment for age did not substantially change the results (data not shown).

For the whole sample of 550 patients who were alive and living in Denmark at the 5-year follow-up, we were able to analyse differences in the number of days admitted to psychiatric hospital and the number of days in psychiatric housing facilities for the patients with cannabis use at entry compared with those with no cannabis use. For this total sample, we do not have data on cannabis use after 5 years, due to drop-out; therefore, we can only analyse the association with cannabis use at entry. Patients with cannabis use at entry spent 221 (S.D.=271) days in hospital compared with 180 (S.D.=251) days for the other patients during the 5 years ($p=0.1$), and 167 (S.D.=377) *v.* 114 (S.D.=302) days in psychiatric housing facilities ($p=0.1$).

Discussion

At the 5-year follow-up, cannabis users had higher scores on the psychotic dimension and a lower level of GAF social functioning compared with the patients with no cannabis use. Those who stopped using cannabis between entry and 5-year follow-up had a significantly lower level of psychotic symptoms at 5-year follow-up compared with those who had a continuous use of cannabis. As recommended by the previously mentioned review from 2008 (Zammit *et al.* 2008), we included baseline values of the outcome measures as covariates. We found that the association with severity of psychotic symptoms was significant, even after controlling for the baseline level of psychotic symptoms, and it was also significant when adjusted for insufficient antipsychotic medication and age. On this basis, we can conclude that continued frequent cannabis use is associated with a higher level of psychotic symptoms, and this is only partly explained by a larger proportion of cannabis users having insufficient antipsychotic medication. Therefore, it is likely that the higher level of psychotic symptoms is a separate effect of continued use of cannabis.

We found a significantly lower level of adaptation to school, measured as the academic dimension of the PAS, among those who used cannabis at entry compared with no use. The most likely explanation for this finding is that young people with poor academic performance are more likely to start using cannabis (Macleod *et al.* 2004). However, it is also possible that some had started cannabis use very early and that the use affected their school performance.

Our findings regarding effects of cannabis use on negative symptoms are contradictory. When analysed as a continuous outcome measure, we cannot find any significant effect of continuous use of cannabis, but analyses of remission as a dichotomous outcome indicate that compared with users, non-users of cannabis at 5-year follow-up have better chances of achieving remission of negative symptoms. However, this could be a spurious finding, since the results are contradictory and the number of cases is rather low.

Even though the differences in use of psychiatric beds and supported psychiatric housing facilities in the 5-year follow-up period did not reach statistical significance due to large variation, it cannot be overlooked that frequent cannabis use at entry is associated with higher levels of service use in the 5-year follow-up period.

Strengths

We were able to utilize data from a large, thoroughly assessed cohort of patients with first-episode psychotic disorder followed up after 5 years, and to include clinical conditions at entry in the study. We could also include information about antipsychotic medication in our analyses of associations between clinical conditions and pattern of cannabis use.

Use of cannabis was evaluated according to chapter 12, item 12.007 in the SCAN interview. We have recently shown that in non-penalizing settings, self-reports are a reliable measure of cannabis use (Hjorthoj *et al.* 2012*a*,*b*).

Limitations

The variables we used as determinants in the analyses were rather crude in that we only separated cannabis

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

Table 3. *Clinical and social outcome after 5 years among 314 patients with first-episode psychosis included in the OPUS trial, divided into abstainers, stoppers, starters and continuers based on their pattern of cannabis use*

	n	Mean (S.D.)	(95% CI)	*p*
Psychotic dimension				
Abstainers	185	1.3 (1.6)	(1.0–1.5)	<0.01
Stoppers	66	1.3 (1.6)	(0.8–1.6)	
Starters	12	1.9 (1.7)	(1.0–2.8)	
Continuers	24	2.4 (1.6)	(1.8–3.0)	
Disorganized dimension				
Abstainers	186	0.4 (0.8)	(0.3–0.6)	0.7
Stoppers	68	0.4(0.6)	(0.2–0.5)	
Starters	12	0.6 (0.7)	(0.2–1.1)	
Continuers	24	0.5 (0.6)	(0.2–0.8)	
Negative dimension				
Abstainers	186	1.7 (1.4)	(1.5–1.9)	0.6
Stoppers	68	1.8 (1.5)	(1.5–2.1)	
Starters	12	2.2 (1.1)	(1.4–2.9)	
Continuers	24	1.9 (1.2)	(1.4–2.5)	
GAF, symptoms dimension				
Abstainers	198	53.8 (17.3)	(51.4–56.1)	0.1
Stoppers	73	56.3 (17.0)	(52.4–60.2)	
Starters	11	46.3 (16.9)	(36.2–56.4)	
Continuers	25	49.1 (16.9)	(4.4–55.8)	
GAF, social dimension				
Abstainers	198	55.4 (17.7)	(52.9–57.8)	0.06
Stoppers	73	57.0 (18.0)	(52.9–61.0)	
Starters	11	45.2 (17.0)	(34.7–55.6)	
Continuers	25	48.6 (18.6)	(41.7–55.5)	
Sufficient antipsychotic medication[a] (%)				
Abstainers	200	(87.0)		0.03
Stoppers	73	(83.6)		
Starters	12	(83.3)		
Continuers	25	(64.0)		
Number of days in hospital during first 5 years				
Abstainers	203	182.8 (288.8)	(135.0–206.7)	0.9
Stoppers	74	207.2 (270.5)	(163.5–351.8)	
Starters	12	194.8 (233.4)	(14.1–341.5)	
Continuers	25	202.0 (314.7)	(41.0–313.7)	
Number of days in hospital, fifth year				
Abstainers	232	20.4 (63.2)	(11.6–29.2)	0.9
Stoppers	41	24.3 (65.6)	(9.7–38.9)	
Starters	11	26.2 (63.1)	(–10.1 to 62.4)	
Continuers	18	31.2 (64.3)	(60–56.3)	
Number of days in supported housing facility during first 5 years				
Abstainers	185	102.7 (313.3)	(53.8–151.6)	0.3
Stoppers	64	139.3 (334.9)	(56.5–222.8)	
Starters	11	113.3 (231.6)	(–87.3 to 313.9)	
Continuers	23	286.4 (531.3)	(147.2–425.1)	
Number of days in supported housing facility, fifth year				
Abstainers	189	27.9 (92.2)	(13.7–42.0)	0.1
Stoppers	64	29.2 (98.7)	(4.8–53.4)	
Starters	11	8.1 (27.4)	(–50.4 to 66.9)	
Continuers	23	64.0 (98.9)	(23.5–104.6)	

S.D., Standard deviation; CI, confidence interval; GAF, Global Assessment of Functioning; abstainers, no use of cannabis at baseline and at 5-year follow-up; stoppers, stopped cannabis use between baseline and 5-year follow-up; starters, started cannabis use between baseline and 5-year follow-up; continuers, used cannabis at baseline and at 5-year follow-up.

[a] Taking prescribed antipsychotic medication or no prescription and not psychotic.

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

Table 4. *Differences in clinical and social outcome after 5 years among 314 patients with first-episode psychosis included in the OPUS trial, divided into abstainers, stoppers and starters versus continuers, based on their pattern of cannabis use*

	Difference	(95% CI)	*p*	Adjusted difference[a]	(adjusted 95% CI[a])	Adjusted *p*[a]
Psychotic dimension						
Abstainers *v.* continuers	–1.13	(–1.81 to –0.45)	0.001	–0.95	(–1.61 to –0.28)	0.006
Stoppers *v.* continuers	–1.18	(–1.93 to –0.44)	0.002	–1.04	(–1.77 to –0.31)	0.006
Starters *v.* continuers	0.52	(–1.62 to 0.58)	0.4	–0.36	(–1.44 to 0.72)	0.5
Negative dimension						
Abstainers *v.* continuers	–0.23	(–0.82 to 0.36)	0.4	–0.11	(–0.70 to 0.50)	0.7
Stoppers *v.* continuers	–0.13	(–0.77 to 0.51)	0.7	–0.03	(–0.67 to 0.78)	0.9
Starters *v.* continuers	0.26	(–0.70 to 1.22)	0.6	0.36	(–0.59 to 0.83)	0.5
Disorganized dimension						
Abstainers *v.* continuers	–0.06	(–0.38 to 0.27)	0.7	0.07	(–0.24 to 0.38)	0.6
Stoppers *v.* continuers	–0.13	(–0.49 to 0.22)	0.5	–0.03	(–0.37 to 0.31)	0.9
Starters *v.* continuers	0.14	(–0.39 to 0.67)	0.6	0.25	(–0.25 to 0.75)	0.3

CI, Confidence interval; abstainers, no use of cannabis at baseline and at the 5-year follow-up; stoppers, stopped cannabis use within the last 5 years; starters, started cannabis use within the last 5 years; continuers, continued use of cannabis throughout the 5 years.

[a] Adjusted for treatment with antipsychotic medication.

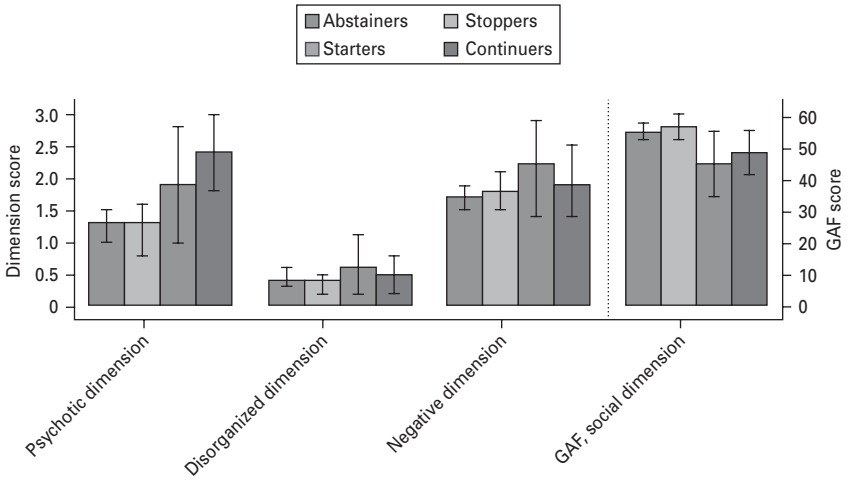

Fig. 1. Clinical and social outcome after 5 years among 314 patients included in the OPUS trial with first-episode psychosis. The patients are divided into abstainers, stoppers, starters and continuers on the basis of their pattern of cannabis use. Values are means, with 95% confidence intervals represented by vertical bars. GAF, Global Assessment of Functioning.

use into no use *versus* any use. Evaluation of dose–response effect could be considered, and maybe also including data on the strength of the cannabis used, as studies have shown that the amount of the active ingredient Δ^9-tetrahydrocannabinol in the cannabis smoked also has been shown to have an impact on psychosis severity (D'Souza *et al.* 2005; Di Forti *et al.* 2009).

Implications

Even though reverse causality cannot be excluded, the baseline differences between the patients with use of cannabis compared with no use justify a warning against the use of cannabis, since it can be associated with triggering psychotic disorder and poor academic performance.

Our study does indicate that cannabis, as such, worsens the risk of having a continuous psychotic condition, as this association was significant even after adjusting for insufficient antipsychotic medication as a mediating factor. Patients with use of cannabis should be offered treatment in order to facilitate reduction or discontinuation of cannabis use, since continued use of cannabis is associated with insufficient

https://doi.org/10.1017/S0033291713000433 Published online by Cambridge University Press

medication, higher level of psychotic symptoms and reduced social functioning, as well as lack of remission.

Acknowledgements

We would like to thank the anonymous reviewers for valuable comments. The project received grants from the Danish Ministry of Health (jr.nr. 96-0770-71), Danish Ministry of Social Affairs, the University of Copenhagen, Copenhagen Hospital Cooperation, the Danish Medical Research Council (jr.nr. 9601612 and 9900734), Slagtermester Wørners Foundation and the Stanley Wada Research Foundation.

Declaration of Interest

None.

References

Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *American Journal of Psychiatry* **162**, 441–449.

Anglin DM, Corcoran CM, Brown AS, Chen H, Lighty Q, Brook JS, Cohen PR (2012). Early cannabis use and schizotypal personality disorder symptoms from adolescence to middle adulthood. *Schizophrenia Research* **137**, 45–49.

Archie S, Rush BR, Akhtar-Danesh N, Norman R, Malla A, Roy P, Zipursky RB (2007). Substance use and abuse in first-episode psychosis: prevalence before and after early intervention. *Schizophrenia Bulletin* **33**, 1354–1363.

Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P (1995). A longitudinal study of symptom dimensions in schizophrenia. Prediction and patterns of change. *Archives of General Psychiatry* **52**, 352–360.

Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, le Quach P, Christensen TO, Krarup G, Jorgensen P, Nordentoft M (2008). Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Archives of General Psychiatry* **65**, 762–771.

Cannon-Spoor E, Potkin SG, Wyatt RJ (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin* **8**, 470–484.

Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, Esterberg ML, Stewart T, Walker EF (2009). Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *American Journal of Psychiatry* **166**, 1251–1257.

D'Souza DC, bi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological Psychiatry* **57**, 594–608.

Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B, Powell J, Murray RM (2009). High-potency cannabis and the risk of psychosis. *British Journal of Psychiatry* **195**, 488–491.

Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, Dingemans PM, Birchwood M, Patterson P, Salokangas RK, Heinimaa M, Heinz A, Juckel G, Graf von Reventlow H, French P, Stevens H, Ruhrmann S, Klosterkötter J, Linszen DH (2012). Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. *Acta Psychiatrica Scandinavica* **125**, 45–53.

Dunn M, O'Driscoll C, Dayson D, Wills W, Leff J (1990). The TAPS Project. 4: An observational study of the social life of long-stay patients. *British Journal of Psychiatry* **157**, 842–8, 852.

Faridi K, Joober R, Malla A (2012). Medication adherence mediates the impact of sustained cannabis use on symptom levels in first-episode psychosis. *Schizophrenia Research* **141**, 78–82.

Häfner H, Riecher-Rössler A, Hambrecht M, Maurer K, Meissner S, Schmidtke A, Fätkenheuer B, Löffler W, van der Heiden W (1992). IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophrenia Research* **6**, 209–223.

Hjorthoj CR, Fohlmann A, Larsen AM, Arendt M, Nordentoft M (2012*a*). Correlations and agreement between delta-9-tetrahydrocannabinol (THC) in blood plasma and timeline follow-back (TLFB)-assisted self-reported use of cannabis of patients with cannabis use disorder and psychotic illness attending the CapOpus randomized clinical trial. *Addiction* **107**, 1123–1131.

Hjorthoj CR, Hjorthoj AR, Nordentoft M (2012*b*). Validity of Timeline Follow-Back for self-reported use of cannabis and other illicit substances – systematic review and meta-analysis. *Addictive Behavior* **37**, 225–233.

Jeppesen P, Petersen L, Thorup A, Abel MB, Ohlenschlaeger J, Christensen TO, Krarup G, Jorgensen P, Nordentoft M (2008). The association between pre-morbid adjustment, duration of untreated psychosis and outcome in first-episode psychosis. *Psychological Medicine* **38**, 1157–1166.

Kamali M, Kelly BD, Clarke M, Browne S, Gervin M, Kinsella A, Lane A, Larkin C, O'Callaghan E (2006). A prospective evaluation of adherence to medication in first episode schizophrenia. *European Psychiatry* **21**, 29–33.

Large M, Sharma S, Compton MT, Slade T, Nielssen O (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of General Psychiatry* **68**, 555–561.

Larsen TK, Friis S, Haahr U, Johannessen JO, Melle I, Opjordsmoen S, Rund BR, Simonsen E, Vaglum PV, McGlashan TH (2004). Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *British Journal of Psychiatry* **185**, 108–115.

Macleod J, Oakes R, Copello A, Crome I, Egger M, Hickman M, Oppenkowski T, Stokes-Lampard H, Davey SG (2004). Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet* **363**, 1579–1588.

McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, Alati R, Williams GM, Bor W, Najman JM (2010). Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Archives of General Psychiatry* **67**, 440–447.

Miller R, Ream G, McCormack J, Gunduz-Bruce H, Sevy S, Robinson D (2009). A prospective study of cannabis use as a risk factor for non-adherence and treatment dropout in first-episode schizophrenia. *Schizophrenia Research* **113**, 138–144.

Moore THM, Zammit S, Lingfjord.Hughes A, Barnes TRE, Jones PB, Lewis G (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319–328.

Mors O, Perto GP, Mortensen PB (2011). The Danish psychiatric central research register. *Scandinavian Journal of Public Health* **39**, 54–57.

Nelson HE (1982). *National Adult Reading Test (NART)*. NFER-Nelson: Windsor.

Nordentoft M, Ohlenschlaeger J, Thorup A, Petersen L, Jeppesen P, Bertelsen M (2010). Deinstitutionalization revisited: a 5-year follow-up of a randomized clinical trial of hospital-based rehabilitation *versus* specialized assertive intervention (OPUS) *versus* standard treatment for patients with first-episode schizophrenia spectrum disorders. *Psychological Medicine* **40**, 1619–1626.

Nordentoft M, Pedersen MG, Pedersen CB, Blinkenberg S, Mortensen PB (2012). The new asylums in the community: severely ill psychiatric patients living in psychiatric supported housing facilities. A Danish register-based study of prognostic factors, use of psychiatric services, and mortality. *Social Psychiatry and Psychiatric Epidemiology* **47**, 1251–1261.

Pedersen CB, Gotzsche H, Moller JO, Mortensen PB (2006). The Danish Civil Registration System. A cohort of eight million persons. *Danish Medical Bulletin* **53**, 441–449.

Pedersen G, Hagtvet KA, Karterud S (2007). Generalizability studies of the Global Assessment of Functioning-Split version. *Comprehensive Psychiatry* **48**, 88–94.

Petersen L, Jeppesen P, Thorup A, Abel MB, Ohlenschlaeger J, Christensen TO, Krarup G, Jorgensen P, Nordentoft M (2005). A randomised multicentre trial of integrated *versus* standard treatment for patients with a first episode of psychotic illness. *British Medical Journal* **331**, 602.

Petersen L, Jeppesen P, Thorup A, Ohlenschlaeger J, Krarup G, Ostergard T, Jorgensen P, Nordentoft M (2007). Substance abuse and first-episode schizophrenia-spectrum disorders. The Danish OPUS trial. *Early Intervention in Psychiatry* **1**, 88–96.

Quach PL, Mors O, Christensen TO, Krarup G, Jorgensen P, Bertelsen M, Jeppesen P, Petersen L, Thorup A, Nordentoft M (2009). Predictors of poor adherence to medication among patients with first-episode schizophrenia-spectrum disorder. *Early Intervention in Psychiatry* **3**, 66–74.

Rubino T, Zamberletti E, Parolaro D (2012). Adolescent exposure to cannabis as a risk factor for psychiatric disorders. *Journal of Psychopharmacology* **26**, 177–188.

Russell AJ, Munro J, Jones PB, Hayward P, Hemsley DR, Murray RM (2000). The National Adult Reading Test as a measure of premorbid IQ in schizophrenia. *British Journal of Clinical Psychology* **39**, 297–305.

Schimmelmann BG, Conus P, Cotton S, Kupferschmid S, McGorry PD, Lambert M (2012). Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. *European Psychiatry* **27**, 463–469.

Schimmelmann BG, Conus P, Cotton SM, Kupferschmid S, Karow A, Schultze-Lutter F, McGorry PD, Lambert M (2011). Cannabis use disorder and age at onset of psychosis – a study in first-episode patients. *Schizophrenia Research* **129**, 52–56.

Sundhedsstyrelsen (2012). *Narkosituationen i Danmark 2012* (ed. Sundhedsstyrelsen), pp. 1–117. Sundhedsstyrelsen (Danish National Board of Health): Copenhagen.

Thorup A, Petersen L, Jeppesen P, Ohlenschlaeger J, Christensen T, Krarup G, Jorgensen P, Nordentoft M (2005). Integrated treatment ameliorates negative symptoms in first episode psychosis – results from the Danish OPUS trial. *Schizophrenia Research* **79**, 95–105.

van Dijk D, Koeter MW, Hijman R, Kahn RS, van den Brink W (2012). Effect of cannabis use on the course of schizophrenia in male patients: a prospective cohort study. *Schizophrenia Research* **137**, 50–57.

WHO (1992). *Life Chart Rating Form. Introduction to the Life Chart Schedule*. World Health Organization: Geneva.

Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N (1990). SCAN: Schedule for Clinical Assessment in Neuropsychiatry. *Archives of General Psychiatry* **47**, 589–593.

Zamberletti E, Prini P, Speziali S, Gabaglio M, Solinas M, Parolaro D, Rubino T (2012). Gender-dependent behavioral and biochemical effects of adolescent delta-9-tetrahydrocannabinol in adult maternally deprived rats. *Neuroscience* **204**, 245–257.

Zammit S, Moore TH, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2008). Effects of cannabis use on outcomes of psychotic disorders: systematic review. *British Journal of Psychiatry* **193**, 357–363.

Zammit S, Owen MJ, Evans J, Heron J, Lewis G (2011). Cannabis, COMT and psychotic experiences. *British Journal of Psychiatry* **199**, 380–385.