Continued Cannabis Use and Outcome in First-Episode Psychosis: Data From a Randomized, Open-Label, Controlled Trial

Gunnar Faber, MD, PhD; Henderikus G. O. M. Smid, PhD; Arthur R. Van Gool, MD, PhD; Lex Wunderink, MD, PhD; Robert J. van den Bosch, MD, PhD; and Durk Wiersma, PhD

ABSTRACT

Objective: Cannabis use has been found to increase the risk of psychosis. It is unclear whether, after a first psychotic episode has occurred, continued cannabis use is associated with poor functional outcome of psychosis.

Method: As part of a randomized, open-label, controlled trial, the association of cannabis use and measures for psychopathology and social role functioning after 2 years of follow-up and for the recently proposed outcome measures of symptomatic remission, functional remission, and clinical recovery was explored in a group of 124 patients suffering from nonaffective first-episode psychosis (diagnosed according to *DSM-IV* and included from a catchment area in the Netherlands of 3.1 million inhabitants from October 2001 through December 2002). Other patient characteristics that were expected to be independently associated with outcome, among them alcohol and other drug use, were assessed at baseline.

Results: Continued cannabis use was not associated with symptomatic or functional remission or clinical recovery. After 2 years, cannabis use was related to certain aspects of social role functioning (economic and social activities; explained variance 5.6% and 8.4%, respectively) but not to psychopathology (Positive and Negative Syndrome Scale Positive, Negative, or General symptoms).

Conclusions: Our findings support the notion that continued cannabis use after the onset of a first-episode psychosis is correlated with worse social outcome and should be discouraged whenever possible, but its role in outcome is modest in comparison to other factors.

Trial Registration: Nederlands Trial Register: http://www.trialregister.nl (ID: NTR 374).

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Corresponding author: *Gunnar Faber, MD, Yulius, Mental Health Institute, Hellingen 21, Dordrecht, 3311 GZ, Netherlands (g.faber@yulius.nl).*

Cannabis use is widespread in Western countries. In the Netherlands, in 2007 and 2008, on average 32% of youth between 15 and 25 years of age reported having at least once used cannabis, and 11% reported having used cannabis in the previous 30 days.[1]

Although the existing evidence is consistent with the view that cannabis increases the risk of psychosis in cannabis users, independent of confounding bias and apart from transient intoxication effects, less is known about whether continued cannabis use—after a firm diagnosis of first-episode psychosis has been established—negatively influences long-term outcome.[2,3] If continued cannabis use is found to contribute to a worsening of long-term outcome, there would be a strong argument to persuade first-episode patients to stop cannabis use.[4,5] Notably, several studies suggest increased cannabis use following onset of psychosis.[6,7]

In a systematic review of the literature on this subject by Zammit et al,[8] cannabis use was consistently associated with increased relapse and nonadherence. Associations with other outcome measures (such as severity of symptoms and response to treatment) were more disparate. Few studies adjusted for baseline illness severity, and most made no adjustment for other potentially important confounders such as alcohol use. Adjusting for even a few confounders often resulted in substantial attenuation of results.

Furthermore, the studies mainly focused on symptomatology, whereas outcome measures for schizophrenia should be multidimensional and incorporate both functional and clinical parameters.[9]

We addressed these issues in a 2-year follow-up study of patients with nonaffective first-episode psychosis. We first investigated whether continued cannabis use was related to the recently proposed outcome measures of symptomatic remission, functional remission, and clinical recovery, each of which is dichotomous.[10,11] The second research question was whether continued cannabis use was correlated with continuous measures of psychopathology (assessed with the Positive and Negative Syndrome Scale; PANSS)[12] or social role functioning (measured with the Groningen Social Disabilities Schedule; GSDS)[13,14] at 2-year follow-up.

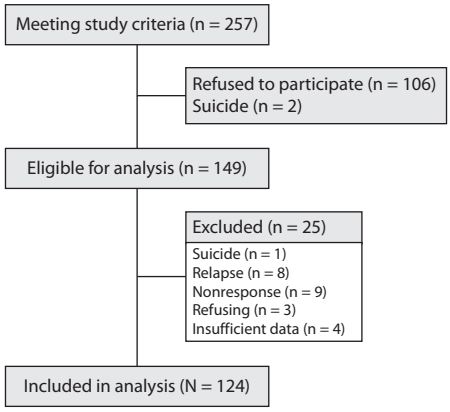
METHOD

Patient Sample

The study is part of a 2-year prospective study, a randomized, open-label, controlled trial, of the effects of maintenance antipsychotic treatment versus guided discontinuation in first-episode nonaffective psychosis. The cohort was drawn from a catchment area of 3.1 million inhabitants in the Netherlands from October 2001 through December 2002. Assessments were conducted at the time of inclusion (baseline, T0) and after 6 (T6), 15 (T15), and 24 (T24) months.[11,15]

The patients included in this study were first-episode patients, aged 18 to 45 years, who had never received antipsychotics for longer than 3 months before inclusion, showing a sufficient treatment response to positive symptoms (a maximum score of 4 on no more than 1 item on the

Figure 1. Patient Flow Diagram



positive subscale of the PANSS and no relapses) within the first 6 months of treatment. Patients were largely recruited as outpatients and the patients that were recruited during hospitalization usually continued their treatment as outpatients (as is common practice in the Netherlands). The 7 participating sites were part of regional mental health care institutions, except for the Department of Psychiatry of the University Medical Center Groningen. Patients were asked to participate as soon as they were able to understand the consequences of participation. After providing written informed consent, the patients were diagnosed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[16] Only patients with schizophrenia and other nonaffective psychotic disorders, according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, were included.

Of 257 treatment-naive first-episode patients who met the study criteria, 149 (58%) gave written informed consent. Eventually, 124 of these 149 patients (83%) were included in the present study (Figure 1). There were no differences between participants and nonparticipants regarding sex, age at first contact, marital status, living situation, and illicit drug use.

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen, and it was registered at Nederlands Trial Register: http://www.trialregister.nl (ID: NTR 374).

Baseline and Follow-Up Assessments

Sociodemographic and psychopathologic variables (sex, age at onset of psychosis, diagnosis, highest level of education, duration of untreated psychosis, and drug and alcohol use) were recorded at the time of inclusion in the study (T0). Duration of untreated psychosis was assessed during the SCAN interview and defined as the time between the first manifestation of any positive psychotic symptom and the start of antipsychotic treatment. Psychopathology (PANSS) was assessed at T0 and at T6, T15, and T24, and social role functioning (GSDS) at T0, T15, and T24. Furthermore, the research nurse gathered information from the clinician (and when deemed necessary also from the patient and family) on (change in) medication status (type, dosage, and adherence), social functioning, and possible relapses on a monthly basis. Medication adherence was calculated as a combination of dose and frequency of use during each previous month (eg, 50% meaning that the patient took the full amount of the prescribed medication during half of the time or half the amount during the full time) and expressed as the mean over the whole study period.

Clinical Points

- Cannabis use should be discouraged after onset of a first-episode psychosis.
- Motivational interviewing and cognitive-behavioral therapy or psychoeducation can be effective.
- Patients can be unaware of the long-term detrimental effects because of perceived short-term positive effects of cannabis.

Assessment of Cannabis, Drug, and Alcohol Use

Cannabis, other drugs, and alcohol use at the time of inclusion and in the period prior to inclusion was assessed by means of the SCAN interview. The illicit drugs section of this semistructured interview–based instrument measures use of different drugs, ranging from none to daily use, during at least 1 month, in the previous year.

At baseline, 65.3% had never used cannabis in this observational period, 34.7% had used any amount of cannabis prior to inclusion, and 18.5% of the total sample had used cannabis on a daily basis during more than a month.

The use of other drugs (among which are cocaine, stimulants, ecstasy, and hallucinogens) was limited to 13 patients, who often used drugs from several categories. At baseline, 6 patients had used cocaine at least once a month, 7 had used stimulants at least once a month, and 10 had used ecstasy or hallucinogens at least once a month.

The alcohol section of the SCAN measures, among others, the frequency (from less than once a month to daily during at least a month) and the mean daily amount (from 1 to 2 to more than 25 standard quantities) of alcohol use in the previous year. In the year before baseline, 33.9% of patients had not used alcohol, 66.1% had used any amount of alcohol, and 8.1% of the total had used alcohol at least daily during at least 1 month in that period.

At follow-up and at T6, T15, and T24, cannabis use was assessed by means of a semistructured interview with the patient by a research nurse (each assessment covering the previous period) with use of a 7-point scale, ranging from no use (0), less than once a month (1), once a month (2), more than once a month (3), once a week (4), more than once a week (5), once daily (6), to more than once daily (7).

Next, we calculated the mean monthly use (for instance, once a week was scored as 4 times per month) for each patient during the observation period. During the 2-year follow-up, 26 of 124 patients (21%) continued cannabis use.

Symptomatic Remission, Functional Remission, and Clinical Recovery

Symptomatic outcome, *functional outcome*, and *clinical recovery* were defined according to the criteria proposed by Wunderink et al.[11]

Criteria for symptomatic remission were adopted from Andreasen et al,[10] incorporating a selection of 8 items from the PANSS with an observational period of the last 9 months of a 2-year follow-up period. All relevant item scores had to be 3 (mild) or less on a scale ranging from 1 (not present) to 7 (severe) at T15 and T24, without symptomatic relapses in this intermediary period.

Functional remission was assessed with the use of the GSDS[13,14] within the same time frame. Social role functioning in this instrument is measured against normative expectations in a certain cultural context. Social disabilities are assessed by means of a semistructured, investigator-based interview with the patient and, when deemed necessary, corroborated with information from clinicians, family, and other relevant caregivers. The GSDS measures social functioning and adjustment over the last 4 weeks in 8 social roles, each of which is composed of different role dimensions: Self-Care, Kinship (GSDS-KD), Family Relationships, Partner Relationships, Community Integration (GSDS-CI), Relationship With Peers, Vocational Role, and Parental Role. In this study, the Parental Role was left out because of limited applicability. A disability was rated by the investigator on a 4-point scale from no (0), minimal (1), obvious (2), and serious (3) disability. For the definition of functional remission, it was decided that a patient should function adequately in social roles with none or only a minimal disability in any of the 7 roles (not allowing a score of 2 or 3 on any GSDS role) at T15 and T24, without functional relapses in the intermediary period.

Clinical recovery was defined as the combination of both symptomatic and functional remission.

Psychopathology and Social Role Functioning

The PANSS Positive (PANSS-P), Negative (PANSS-N), and General (PANSS-G) scores, after 2-year follow-up, were used as continuous outcome measures for psychopathology, and the 7 GSDS roles scores, after 2-year follow-up, were used as continuous outcome measures for social role functioning.

Statistical Analysis

Analyses were carried out with the statistical package SPSS[17] (IBM, Armonk, New York).

Pearson χ^2 test (2-sided) was used to analyze differences between the number of cannabis users and nonusers who achieved symptomatic remission, functional remission, or clinical recovery. In a post hoc analysis, regarding the association between cannabis use and relapse and nonadherence, differences between continued cannabis users and nonusers were analyzed using Pearson χ^2 tests (2-sided) for categorical variables (any relapse, diagnosis of schizophrenia) and Student *t* tests (2-tailed) for continuous variables (months in relapse, percentage of medication adherence, PANSS-P, PANSS-N, and PANSS-G scores).

Table 1. Sample Demographic and Clinical Characteristics of 124 Patients With Nonaffective First-Episode Psychosis

Characteristic	Value
Sex, male, %	68.5
Age at onset, mean ± SD, y	25.7 ± 6.7
Education level, L/S/H, %	23.4/55.6/21.0
Diagnosis, %	
Schizophrenia	45.2
Schizophreniform disorder	23.4
Schizoaffective disorder	5.6
Brief psychotic disorder	2.4
Delusional disorder	12.1
Psychotic disorder NOS	11.3
Duration of untreated psychosis, mean ± SD, d	266 ± 537
Haloperidol equivalents at 24 mo, mean ± SD, mg	2.46 ± 2.06

Abbreviations: H = higher education or university, L = no or lower education, NOS = not otherwise specified, S = secondary education.

To identify factors predicting symptomatic remission, functional remission, or clinical recovery, a binary logistic regression analysis with forward selection (likelihood ratio) was applied, with these outcome measures as the dependent variable and continued mean cannabis use, other drug and alcohol use at T0, haloperidol equivalents at T24, PANSS-P, PANSS-N, and PANSS-G scores and GSDS sum scores at T0, sex, education level, schizophrenia diagnosis, and duration of untreated psychosis as independent variables.

To identify factors predicting PANSS-P, PANSS-N, and PANSS-G or GSDS role scores at T24, a linear regression analysis with forward selection was applied with these outcome measures as dependent variable and continued mean cannabis use and the other variables mentioned above as independent variables.

RESULTS

Main characteristics of the patient sample are shown in Table 1. Patients used atypical antipsychotics in more than 95% of cases (mainly risperidone and olanzapine). Medication adherence was high, with an estimated mean of around 86% of the prescribed medication taken adequately.

In total, 65 patients (52.4%) fulfilled the criteria for symptomatic remission (13 of the 26 continued cannabis users and 52 of the 98 nonusers), whereas 32 patients (25.8%) fulfilled the criteria for functional remission (6 of the 26 continued cannabis users and 26 of the 98 nonusers) and 24 patients (19.4%) fulfilled the criteria for clinical recovery (5 of the 26 continued cannabis users and 19 of the 98 nonusers). There was no significant difference between the number of continued cannabis users and nonusers who achieved symptomatic remission ($\chi^2_1 = 0.077$, $P = .781$), who achieved functional remission ($\chi^2_1 = 0.128$, $P = .721$), or who achieved clinical recovery ($\chi^2_1 = 0.000$, $P = .986$).

Table 2 shows the main results of the binary logistic regression analyses. No association was found between mean cannabis use and the 3 outcome measures of symptomatic remission, functional remission, or clinical recovery.

Table 2. Binary Logistic Regression Analyses on Symptomatic and Functional Remission and Clinical Recovery

Model/Variable		B	SE	*P*	OR	Lower CI	Upper CI	R^2	Model χ^2	*P* (χ^2)
Symptomatic Remission										
1	Constant	0.67	0.26	.01	1.96			0.12	11.59	.00
	Schizophrenia diagnosis at T0	−1.26	0.38	.00	0.28	0.14	0.60			
2	Constant	2.25	0.63	.00	9.50			0.20	20.37	.00
	Schizophrenia diagnosis at T0	−1.29	0.39	.00	0.28	0.13	0.60			
	PANSS-N score at T0	−0.11	0.04	.00	0.89	0.82	0.97			
3	Constant	2.64	0.67	.00	13.96			0.24	24.59	.00
	Schizophrenia diagnosis at T0	−1.11	0.41	.01	0.33	0.15	0.73			
	Haloperidol equivalents at T24	−0.21	0.10	.05	0.81	0.66	1.00			
	PANSS-N score at T0	−0.11	0.04	.01	0.89	0.83	0.97			
Functional Remission										
1	Constant	0.40	0.48	.40	1.50			0.13	11.73	.00
	GSDS sum score at T0	−0.19	0.06	.00	0.83	0.73	0.93			
2	Constant	0.45	0.49	.35	1.57			0.18	15.71	.00
	Use of hallucinogens and/or ecstasy at T0	0.48	0.24	.05	1.61	1.01	2.57			
	GSDS sum score at T0	−0.22	0.06	.00	0.81	0.71	0.92			
Clinical Recovery										
1	Constant	−0.09	0.51	.87	0.92			0.11	8.42	.00
	GSDS sum score at T0	−0.18	0.07	.01	0.84	0.74	0.95			
2	Constant	−0.02	0.52	.97	0.98			0.17	14.14	.00
	Use of hallucinogens and/or ecstasy at T0	0.59	0.24	.02	1.80	1.11	2.91			
	GSDS sum score at T0	−0.21	0.07	.00	0.81	0.70	0.93			
3	Constant	0.23	0.54	.67	1.26			0.28	24.23	.00
	Use of hallucinogens and/or ecstasy at T0	0.56	0.27	.04	1.75	1.03	2.98			
	Duration of untreated psychosis	−0.01	0.00	.13	0.99	0.99	1.00			
	GSDS sum score at T0	−0.18	0.07	.01	0.84	0.73	0.97			

Abbreviations: GSDS = Groningen Social Disabilities Schedule, OR = odds ratio, PANSS-N = Positive and Negative Syndrome Scale-Negative subscale.
Symbols: T0 = baseline, T24 = 24 months.

No diagnosis of schizophrenia and a lower PANSS-N score, both at baseline, and less antipsychotic use at T24, were positively associated with symptomatic remission; a lower GSDS sum score and more hallucinogen or ecstasy use, both at baseline, were positively associated with functional remission, whereas a lower GSDS sum score and more hallucinogens or ecstasy use, both at baseline, and a shorter duration of untreated psychosis were positively associated with clinical recovery.

In the linear regression analyses, mean cannabis use during 2-year follow-up was not associated with scores on PANSS-P, PANSS-N, or PANSS-G after 24 months. We did find a significant correlation between more mean cannabis use during the 2-year follow-up and a worse GSDS kinship subscale (GSDS-KS) and GSDS community integration subscale (GSDS-CI) score after 24 months but not between more or less cannabis use and the GSDS self-care, family relationship, partner relationships, relationship with peers, or vocational role scores after 24 months.

Table 3 shows the main results of the regression analyses regarding GSDS-KS and GSDS-CI after 24 months. The explained variance of mean continued cannabis use was 8.4% (R^2 model 1) for GSDS-KS and 5.6% (ΔR^2 model 2) for GSDS-CI.

Besides cannabis use during follow-up, higher (worse) GSDS sum scores at baseline and longer duration of untreated psychosis were associated with higher (worse) scores on GSDS-KS. Cannabis use during follow-up, higher GSDS sum scores at baseline, and a diagnosis of schizophrenia at baseline were associated with higher scores on GSDS-CI.

The explained variance (R^2 model 3) of all these predictors was 17.6% for GSDS-KS and 20.6% for GSDS-CI.

DISCUSSION

An earlier report did not show an association between baseline cannabis abuse and clinical recovery after 2 years.[11] In extension to this finding, also continued mean cannabis use does not appear to influence the rates of (symptomatic or functional) remission and clinical recovery.

With regard to the second study question, concerning the correlation between continuous variables for both prediction and outcome, we first found that there was no significant correlation between mean cannabis use over the 2-year follow-up and PANSS-P, PANSS-N, and PANSS-G scores after 2 years. The absence of a detrimental effect of cannabis on psychopathologic symptoms is consistent with some but not all of the previous studies.[8] The association between not having a diagnosis of schizophrenia at baseline, lower PANSS-N scores at baseline, and achieving symptomatic remission is consistent with earlier findings.[18,19] The finding that patients who achieved symptomatic remission used fewer antipsychotics possibly implies that this type of outcome measure is less dependent on antipsychotic treatment. The association between more hallucinogen or ecstasy use and achieving functional remission and clinical recovery is probably spurious and due to the very limited number of patients using these drugs. On the other hand, possibly, patients using these drugs are inclined to have more social activities. We found no indication that the psychosis in the

Table 3. Multiple Regression Analyses on Groningen Social Disabilities Schedule Kinship and Community Integration Roles

Model/Variable		B	SE	Lower CI	Upper CI	β	*t*	*P*	R^2	Δ R^2	Model *P*
Kinship											
1	Constant	0.58	0.07	0.45	0.72		8.52	.000	0.084		.001
	Cannabis use[a]	0.02	0.01	0.01	0.04	0.29	3.35	.001			
2	Constant	0.21	0.15	−0.08	0.50		1.42	.157		0.059	.005
	Cannabis use[a]	0.03	0.01	0.01	0.04	0.30	3.54	.001			
	GSDS sum score at T0	0.04	0.02	0.01	0.07	0.24	2.89	.005			
3	Constant	0.18	0.14	−0.11	0.46		1.24	.219		0.032	.033
	Cannabis use[a]	0.02	0.01	0.01	0.04	0.27	3.15	.002			
	GSDS sum score at T0	0.04	0.02	0.01	0.07	0.22	2.67	.009			
	Duration of untreated psychosis	0.00	0.00	0.00	0.00	0.18	2.16	.033			
Community integration											
1	Constant	0.18	0.16	−0.14	0.51		1.12	.263	0.110		.000
	GSDS sum score at T0	0.07	0.02	0.03	0.10	0.33	3.89	.000			
2	Constant	0.11	0.16	−0.21	0.43		0.66	.512		0.056	.005
	GSDS sum score at T0	0.07	0.02	0.04	0.10	0.34	4.10	.000			
	Cannabis use[a]	0.02	0.01	0.01	0.04	0.24	2.85	.005			
3	Constant	0.03	0.16	−0.29	0.35		0.19	.846		0.040	.016
	GSDS sum score at T0	0.06	0.02	0.03	0.09	0.29	3.52	.001			
	Cannabis use[a]	0.02	0.01	0.01	0.04	0.23	2.80	.006			
	Schizophrenia[b]	0.35	0.14	0.07	0.63	0.20	2.45	.016			

[a]Mean continued cannabis use during 2-year follow-up. [b]Diagnosis of schizophrenia at baseline.
Abbreviation: GSDS = Groningen Social Disabilities Schedule.
Symbol: T0 = baseline.

ecstasy-using group was drug-related (ie, ecstasy users, compared to nonusers, did not have statistically significant fewer diagnoses of schizophrenia; an earlier age at onset of psychosis; a shorter duration of untreated psychosis; lower PANSS-P, PANSS-N, or PANSS-G scores at baseline; or a lower GSDS total score at baseline and did not use fewer antipsychotics at baseline).

We secondly found a significant correlation between the mean cannabis use over the 2-year follow-up and 2 of the 7 social functioning role scores after 2 years as measured with the GSDS. Notably, alcohol use at baseline was not correlated with these outcomes.

The different role dimensions of the GSDS-KS are social activities and contribution to the economy when living together and, when living alone, independent living skills and economic independence. The GSDS-CI explores interest in the social environment, participation in social events and membership of clubs/societies, and being considerate of others.

The association between better GSDS baseline sum scores and functional remission and between GSDS-KS and GSDS-CI after 2 years implies that social role functioning is relatively uninfluenced by other factors such as psychopathology and shows that baseline GSDS sum scores are not independent of GSDS roles scores after 2 years. Baseline diagnosis of schizophrenia and duration of untreated psychosis were strongly interdependent: a diagnosis of schizophrenia implied a minimum duration of illness before treatment of 6 months. The association between both longer duration of untreated psychosis and a diagnosis of schizophrenia at baseline and worse social role functioning is consistent with earlier findings.[18,19]

In summary, our findings may suggest any of the following 3 possibilities: (1) that continued cannabis use in first-episode patients may lead to less economic and social activity, especially in patients with schizophrenia (or a long duration of untreated psychosis); (2) that less economic and social activity in these patients may lead to continued cannabis use; or (3) that an as-yet unknown third factor may lead to both continued cannabis use and less economic and social activity of these patients.

Furthermore, our findings may seem at odds with the findings of Zammit et al,[8] who found an increased risk of relapse and of nonadherence in patients with psychosis who were also cannabis users. Since we were primarily interested in the association between cannabis use and symptomatic and functional outcome, relapse and nonadherence were not primary endpoints of our study. Relapse and nonadherence are undeniably important. We therefore performed 2 post hoc analyses. The first showed that there was no significant difference between users and nonusers in relapse rate (67% vs 69% who did not relapse; $\chi^2_1 = 0.033$, $P = .86$), months in relapse (0.58 vs 0.62; $t_{122} = -0.126$, $P = .90$), and percentage of medication adherence (85% vs 86.5%; $t_{122} = -0.295$, $P = .77$). Zammit et al[8] pointed at the possible role of illness-severity as moderating the association between cannabis use and relapse rate. Our second post hoc analysis therefore looked into this and showed no significant difference between users and nonusers in PANSS-P (10.3 vs 10.3; $t_{122} = 0.108$, $P = .91$), PANSS-N (14.3 vs 13.4; $t_{122} = 0.796$, $P = .428$), PANSS-G (28.0 vs 25.4; $t_{122} = 1.739$, $P = .08$) scores, all at baseline, and a diagnosis of schizophrenia (54% vs 43%; $\chi^2_1 = 1.002$, $P = .32$). Together, these post hoc analyses suggest that, as pointed out by Zammit et al,[8] illness severity in some studies may have indeed influenced the association between cannabis use and risk of relapse or nonadherence.

Although relationships were found between continued cannabis use and social outcome, our findings suggest that

continuation of cannabis use does not seem to influence the prognosis of psychotic disorders decisively and that the damage by cannabis is inflicted in earlier stages, prior to clinical manifestation of psychosis or around psychosis onset.[3,20]

The negative effects of continued cannabis use on certain components of social outcome might bear a relationship with the effects of cannabis on neurocognition. The main psychoactive component of cannabis, delta-tetrahydrocannabinol (THC), is thought to impact on brain functioning by disrupting the normal function of endocannabinoids on the cannabinoid 1 receptor and ultimately to increase dopamine release in the striatum, resulting in psychotic symptoms[21] (challenged by Stokes et al[22]). However, at the same time, decreased dopamine functioning in the prefrontal cortex may lead to worse neurocognitive functioning,[23] which, in turn, has been shown to be associated with worse social outcome.[18,19,24–27]

The reliability of self-report measures to accurately assess substance use can be questioned. However, there is evidence that self-reported cannabis use is more sensitive than collateral reports, laboratory tests (blood, urine, hair, and saliva), and medical examinations across a range of populations, including first-episode patients with comorbid substance use disorders.[28–30] Additionally, cannabis use is legally tolerated in the Netherlands and not very controversial. Therefore, underreporting is less likely in this study. Nonetheless, we did not have a more precise measure of the total amount of THC exposure (which is also dependent on the strength of the cannabis used) that could possibly have resulted in more informative results. The same applies to the measures of other drug use and alcohol use.

Furthermore, we were not able to address the direct effects of cannabis on inducing psychosis in our study.

One of the strengths of this study was a low attrition rate, with complete data available from 83% of the included patients after 24-month follow-up. Other strengths include the closely and extensively monitored first-episode patient sample and the comprehensive assessments, including most of the known possible confounders. The limited use of other illicit drugs was another strength that allowed us to examine the effect of cannabis on outcome.

In conclusion, our findings show that continued cannabis use after onset of a first psychosis is associated with certain aspects of social outcome. Because of the limited contribution of continued cannabis use to the outcome in first-episode psychosis, however, other factors must play a role in the outcome. In this study, we found that a diagnosis of schizophrenia and longer duration of untreated psychosis in particular were also correlated with worse outcome. A longer duration of untreated psychosis is an established predictor of worse outcome.[31,32] Our results support the notion that cannabis use in first-episode psychosis should be discouraged, in view of the grave consequence of the disorder, the negative influence on social functioning, and the absence of other influenceable factors with the exception of duration of untreated psychosis. Furthermore, one cannot exclude the possibility that the pathogenic effects of cannabis on the brain extend beyond the time period preceding the clinical manifestation of psychosis.

Because patients are first unaware of the detrimental effects of cannabis use, but prone to use cannabis because of short-term perceived positive effects,[33] special attention needs to be directed to persuading first-episode patients to stop or at least diminish cannabis use. A combination of motivational interviewing and cognitive-behavioral therapy but also simple interventions such as psychoeducation has been shown to be effective for patients with first-episode psychosis and comorbid cannabis misuse.[6,34,35]

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

Author affiliations: Yulius, Mental Health Institute, Dordrecht, The Netherlands (Drs Faber and Van Gool); Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (Drs Smid, van den Bosch, and Wiersma); and GGZ-Friesland, Mental Health Institute, Leeuwarden, The Netherlands (Dr Wunderink).

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