Schizophrenia Bulletin vol. 42 no. 3 pp. 619–625, 2016
doi:10.1093/schbul/sbv154
Advance Access publication November 4, 2015

Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study

Jennifer L. Seddon*[,1], Max Birchwood[2], Alex Copello[3,4], Linda Everard[4], Peter B. Jones[5], David Fowler[6], Tim Amos[7], Nick Freemantle[8], Vimal Sharma[9,10], Max Marshall[11], and Swaran P. Singh[2]

[1]National Drug & Alcohol Research Centre, UNSW, Sydney, Australia; [2]Mental Health and Wellbeing Warwick Medical School, University of Warwick, Coventry, UK; [3]School of Psychology, University of Birmingham, Birmingham, UK; [4]The Early Intervention Service, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK; [5]Department of Psychiatry, University of Cambridge and CAMEO, Cambridge and Peterborough NHS Foundation Trust, Cambridge, UK; [6]Department of Psychology, University of Sussex, Brighton, UK; [7]Academic Unit of Psychiatry, University of Bristol, Bristol, UK; [8]Department of Primary Care and Population Health, UCL Medical School (Royal Free Campus), London, UK; [9]Early Intervention Service, Cheshire and Wirral NHS Foundation Trust, Chester, UK; [10]Faculty of Health and Social Care, University of Chester, Chester, UK; [11]School of Medicine, University of Manchester, Manchester, UK

*To whom correspondence should be addressed; National Drug & Alcohol Research Centre, UNSW, Sydney 2052, Australia; tel: 61-2-9385-0357, fax: 61-2-9385-0222, e-mail: jennifer.l.seddon@gmail.com

Objective: **The use of cannabis during the early stage of psychosis has been linked with increased psychotic symptoms. This study aimed to examine the use of cannabis in the 12 months following a first-episode of psychosis (FEP) and the link with symptomatic course and outcome over 1 year post psychosis onset.** ***Design and Setting:*** **One thousand twenty-seven FEP patients were recruited upon inception to specialized early intervention services (EIS) for psychosis in the United Kingdom. Participants completed assessments at baseline, 6 and 12 months.** ***Results:*** **The results indicate that the use of cannabis was significantly associated with increased severity of psychotic symptoms, mania, depression and poorer psychosocial functioning. Continued use of cannabis following the FEP was associated with poorer outcome at 1 year for Positive and Negative Syndrome Scale total score, negative psychotic symptoms, depression and psychosocial functioning, an effect not explained by age, gender, duration of untreated psychosis, age of psychosis onset, ethnicity or other substance use.** ***Conclusion:*** **This is the largest cohort study of FEP patients receiving care within EIS. Cannabis use, particularly "continued use," was associated with poorer symptomatic and functional outcome during the FEP. The results highlight the need for effective and early intervention for cannabis use in FEP.**

Key words: cannabis use/first-episode psychosis/psychotic symptoms/prospective study

Introduction

Psychosis is estimated to affect more than 3% of the population over a lifetime.[1] The early stage, or first-episode of psychosis (FEP) is regarded as a "critical period," important in determining the long-term outcome of psychosis.[2] Loss of functioning and social disability occurs during the prodrome in adolescence and during the first 2–3 years of illness, and plateaus thereafter.[3,4] In addition, a longer duration of untreated psychosis (DUP) is associated with poorer functioning and quality of life as well as increased symptoms, including positive psychotic symptoms.[5]

There is much unexplained variation in outcome in FEP,[1] therefore a greater understanding of the factors that may be prognostic of outcome in FEP is important. One of these is the use of cannabis. Cannabis is widely used among people with psychosis,[6] and in FEP the rate of current cannabis use has been found to range from 19% to 57%.[7–12] Paradoxically, the use of cannabis has been associated with less severe cognitive deficits among people with psychosis,[13] but increased psychiatric symptomatology. Research in FEP samples suggest that cannabis use may be associated with increased positive symptoms[14,15] and increased rates of psychotic relapse,[16,17] whilst the cessation of cannabis use has been linked with significant improvements in positive and negative psychotic symptoms, general psychopathology and psychosocial functioning.[7,9,11,18] A recent meta-analysis has also found that cannabis use may be associated with a

younger age of psychosis onset.[19] However, the majority of studies that have examined the impact of cannabis use on psychotic symptoms have involved relatively small sample sizes, which may result in a lack of power to detect significant effects. Indeed, in a review of the literature the lack of statistical power in many studies has been acknowledged as a limitation, and this is often further compounded by high levels of attrition in longitudinal studies.[20] Furthermore, many studies have failed to control for potential confounding factors, such as other substance use, which may result in an overestimation of the causal effects of cannabis use in psychosis.[20] Well-designed prospective cohort studies involving large clinical samples are needed to definitively determine whether cannabis use affects symptomatic outcome in FEP.

There is also some evidence to suggest that substance use[21] and cannabis use[22] in FEP may be associated with longer DUP. As DUP is an established prognostic factor for outcome in psychosis,[5] the potential mediating effect of DUP warrants further investigation. A recently published review also suggests a potential association between the use of cannabis and mania: cannabis use may be linked with a younger age of mania onset, more frequent manic episodes and poorer outcome.[23] However, there is little data regarding the impact of cannabis use on mania in FEP.

This article aims to examine the impact of cannabis use on the early course of psychosis, mania, depression and functioning in a large prospective sample of individuals with FEP over a period of 12 months after inception to treatment. We examine this using recent data from the UK National EDEN project, a national, multisite project that evaluated the effect of early intervention services (EIS) for people with FEP.[24]

It was hypothesized that:

Cannabis use, and in particular, the continued use of cannabis, will be associated with greater psychotic symptoms and poorer psychosocial functioning at 12 months post psychosis onset.

Method

The National EDEN project aimed to evaluate the implementation and impact of EIS on young people experiencing FEP. The project was conducted within 5 geographical sites across England (Birmingham, Cambridge, Cornwall, Norwich, and Lancashire). EI services are designed to capture individuals with broad-spectrum non-affective psychosis. FEP in the UK context is broadly defined as the spectrum of psychotic disorders including schizophrenia, schizoaffective disorder, delusional disorder, schizotypal personality disorder, schizophreniform disorder, and brief psychotic disorder. The eligibility criteria for entry into EIS require only that people are aged between 14–35 years of age with a first presentation of psychosis. The sample for this study comprised all consecutive referrals to EIS from August 2005 to April 2009. Written informed consent was obtained after complete description of the study. Ethical approval was received by Suffolk Local Research Ethics Committee, UK (REC reference number: 05/Q0102/44). Details of the study rationale and design are published elsewhere.[24]

Measures

Participants completed assessments at baseline, 6 months and 12 months after inception to EI services, substance use was assessed at baseline and 12 months only. Assessments were conducted by research assistants who were not directly involved in clinical care. Inter-rater reliability was assessed and maintained throughout the study period via a comprehensive training and supervision programme. Furthermore, for measures of Positive and Negative Syndrome Scale (PANSS) and DUP all research staff were required to achieve concordance (kappa or intra-class $r > .75$) with the trainers on standard exemplars.[24]

A complete overview of the assessments used in the National EDEN project is provided in the study protocol.[24] The current study involved using measures of substance use, psychotic symptoms, mania, depression and psychosocial functioning.

Substance Use

Lifetime substance use was assessed via client interview and review of patient records. Current substance use was defined as any use of drugs within the previous 3 months as assessed by a revised version of the Kavanagh Drug Check scale.[25,26] The measure provides information in relation to the quantity, frequency and amount spent on drugs within the previous 3 months. The measure also contains a 12-item scale to assess the level of self-reported problems associated with the use of drugs. The problem scale has demonstrated high internal consistency (0.91), with an optimal cut off score of ≥2 recommended (yielding 97% sensitivity and 84% specificity) in detecting a CIDI diagnosis of abuse or dependence.[26] The measure was revised to include an additional item on the problem scale ("did your use of cannabis in the last three months result in you missing doses of medication?"). Current cannabis use in this study was defined as any use within the previous 3 months. The level of dependence for cannabis was assessed using the Severity of Dependence Scale.[27]

Symptom Measures

1. The PANSS[28] was used to assess the severity of positive and negative symptoms of psychosis as well as the level of general psychopathology.
2. The length of DUP was calculated for all clients upon entry to EIS. DUP was defined as the delay between

the onset of psychosis and the onset of treatment and was calculated using a combination of retrospective assessment of PANSS, a semi-structured interview (pathways to care) and patient records.
3. Mania was assessed using the 11-item Young Mania Rating Scale (YMRS).[29]
4. The level of depression was assessed using the 9-item Calgary Depression Scale for Schizophrenia (CDSS).[30] The scale has a high degree of specificity and is not confounded by the negative or extrapryramidal symptoms of psychosis.
5. Psychosocial functioning was assessed using the Global Assessment of Functioning scale (GAF),[31] a clinician rated scale for evaluating the level of psychological, social and occupational functioning on a continuum from 0 to 100. In line with previous research,[32] two further GAF sub-scales were used; GAF-symptoms and GAF-disability, these were scored along a continuum of 0–90.

Data Analysis

Chi-square was performed to examine change in the proportion of participants reporting the use of cannabis. Change in the level of cannabis dependence and cannabis related problems were assessed using the Wilcoxon Signed-Rank test. Association between the use of cannabis at baseline, and the age of psychosis onset and DUP was assessed using independent samples *t* tests and Mann-Whitney tests respectively.

The association between reported cannabis use at each time point (baseline and 12 months) and the response variable was estimated using generalized mixed models. In the base model the PANSS was the response variable; age, gender, ethnicity, age at psychosis onset, DUP and other substance use were explanatory variables. In addition each subject provided information on the effect of cannabis at both time points, plus any additional effects of cannabis at the 1-year follow-up (through fitting an interaction between phase and cannabis use). Each subject provided data at study entry and 1 year, grouped within a subject using random intercept terms. In other words there were 2 observations included in the model for each subject, which were identified by factors to be either baseline or follow up. The denominator degrees of freedom in the model were derived using the approach derived by Kenward and Rogers.[33] The inclusion of the interaction between treatment phase (1 year), and cannabis use at that phase, was retained in the statistical model where it was associated with a statistically significant improvement in model fit as assessed using Akaike's Information Criterion value.[34] Similar models were performed for each response variable of interest (eg, positive/ negative PANNS, Young Mania, Calgary Depression, GAF disability Scale, GAF Symptom Scale, GAF Total Scale).

Missing data were assumed to be missing not at random and so no imputation was undertaken. The potential mechanism for missing data were examined and we applied the findings of White and Carlin,[35] where that the regression coefficients estimates from a complete records analysis are seen to have negligible bias if, conditional on the model's predictors, the missing data process does not depend on the outcome.

Data were analyzed using SPSS 19.0 and SAS 9.3 (SAS Institute).

Results

Participants

1027 participants were recruited upon entry to EIS for FEP. The sample was predominantly male (69%, $n = 709$), with a mean age of 23 (± 4.9). The majority of the sample were White British (73%, $n = 750$), unemployed (57%, $n = 590$), single (85%, $n = 871$) and living with parents (63%, $n = 649$; table 1).

Table 1. Demographic Characteristics of the National EDEN Sample ($n = 1027$) on Their Inception to Early Intervention Services (EIS)

Gender, *n* (%)	
Male	709 (69)
Female	318 (31)
Mean age, years (*SD*)	23 (*SD* 4.9)
Median age, years	22
Diagnosis, *n* (%)	
Schizophrenia	227 (22)
Other nonaffective psychosis	468 (46)
Affective psychosis	117 (11)
Unknown diagnosis	215 (21)
Ethnicity, *n* (%)	
White	750 (73)
Asian	157 (15)
Black	71 (7)
Mixed	43 (4)
Other	6 (1)
Employment status, *n* (%)	
Unemployed	590 (57)
Student	199 (19)
Working (paid)	189 (18)
Home maker	22 (2)
Other	11 (1)
Working (voluntary)	9 (1)
Data not known	7 (1)
Marital status, *n* (%)	
Single	871 (85)
Cohabiting	61 (6)
Married	61 (6)
Separated	21 (2)
Divorced	8 (1)
Living status, *n* (%)	
With parents/guardian	649 (63)
Other	137 (13)
Alone	130 (13)
With partner	108 (11)
Data not known	318 (0)

There was a 75.7% ($n = 777$) participation at 12 months. There were no significant differences in age ($P = .5$), gender ($P = .7$), psychiatric diagnosis ($P = .08$), or the use of cannabis at baseline ($P = .9$) between participants that remained in the study and those lost to follow-up. An additional 1070 clients from EIS did not consent to take part in the study. There were no significant differences in age (consented: 23.0 ± 4.9 vs non-consenters: 22.7 ± 5.3 years; $P = .1$) or gender (consented: males $n = 709$, females $n = 318$ vs non-consenters: males $n = 705$, females $n = 363$; $P = .2$) between participants that consented and those that refused to take part.

Cannabis Use Over the First 12 Months

At baseline, 64% ($n = 654$) of participants reported lifetime use of illicit drugs, with the use of cannabis accounting for most illicit drug use (93%, $n = 611$). Rates of current substance use other than cannabis were also low (table 2). Cannabis users at baseline were found to be significantly younger than non-users (22.5 ± 4.6 years vs 23.3 ± 5.0 years; $P = .02$), and there was a significant association between cannabis use and gender ($P < .001$), with cannabis use 2.17 times more likely in males.

There was a significant decrease in the use of cannabis between baseline ($n = 279$, 27%) and 12 months ($n = 178$, 18%; $P < .001$), accompanied by a significant decrease in the mean level of dependence (baseline: 4.38 ± 3.9; 12 months: 3.60 ± 3.8; $P = .02$) and the mean level of drug related problems (baseline: 7.63 ± 5.7; 12 months: 4.70 ± 5.2; $P = .03$) among participants that continued to use cannabis over the 12-month period.

Data regarding the use of cannabis at baseline and 12 months was available for 760 participants. This indicates that 504 participants (66.3%), did not use cannabis at either time point, 16.8% ($n = 128$) of participants reported using cannabis at baseline and 12 month follow-up, 10.9% ($n = 83$) of participants stopped using cannabis and 5.9% ($n = 45$) reported starting cannabis use during the 12-month study period.

Cannabis Use, DUP, and Age of Psychosis Onset

The mean length of DUP was 308 days (±632), with a mean age of psychosis onset of 21.33 years (±4.99). Participants using cannabis at baseline were found to have a significantly younger age of psychosis onset (20.81 ± 4.7 years vs 21.57 ± 5.0 years; $P = .03$), and participants using cannabis at baseline may have a longer DUP (358 ± 727 days vs 293 ± 600 days; $U = 90538.50$; $P = .055$).

Table 2. Current Substance Use at Baseline ($n = 1027$)

Substance	*n*
Cannabis	279
Stimulants (eg, amphetamine, ecstasy, crack or cocaine)	110
Sedatives or sleeping tablets (eg, valium)	67
Other drugs	53
Opiates (eg, heroin, morphine, methadone)	19
LSD	17
Inhalants (eg, petrol or glue)	8

Cannabis Use and Psychotic Symptoms

The relationship between the use of cannabis and psychotic symptoms was explored at baseline and 12 months; data for substance use at 6 months was not available, therefore assessments at 6 months could not be included in the model.

The use of cannabis at either baseline or 12-month assessment was found to be associated with significantly higher symptoms in PANSS positive and total scores, mania and GAF symptoms, but not negative symptoms or depression. In line with our hypothesis, there were significant interactions between the use of cannabis and phase for PANSS positive, negative and total scores, depression and GAF disability, GAF symptom and GAF total scores, indicating a significant effect of continued cannabis use (table 3). Thus for the PANSS total score for example, cannabis use at either time point was associated with an increase in the PANSS score at that time point of 3.2 units (95% CI = 0.12 to 6.29). In addition, using cannabis at the 1-year follow-up was associated with an additional 6.42 unit increase in PANSS total score (95% CI = 2.31 to 10.53).

The use of cannabis at baseline or 12 months assessment was found to be associated with a 2.14 higher PANSS positive score (95% CI = 1.41 to 2.88), but the interaction term between cannabis use and phase did not significantly improve model fit and thus was omitted in the final model. The PANSS negative score was not significantly affected at baseline in the presence of cannabis use, but the interaction between use at 12 months and the negative score was statistically significant with an increase of 2.12 points (95% CI = 0.75 to 3.48).

Cannabis use was associated with a worsened Young Mania score, but this did not differ according to phase. Cannabis use at 12 months was associated with substantially worsened Calgary Depression and GAF Disability scores. The GAF disability score was reduced both for the use of cannabis at either time period and additionally at 12 months. While the GAF Total Score was reduced substantially at 12 months but not over both time periods.

These associations were adjusted for age, gender, DUP, age of psychosis onset, ethnicity and other substance use.

Discussion

This is the largest study to examine the link between cannabis use and FEP. The large sample size not only allowed us to detect a relationship between the use of cannabis, and the continued use of cannabis on psychotic symptoms and functioning, but also the magnitude of this effect. Consistent with other evidence[19] this study

Table 3. Cannabis Use and Symptom Severity

Model	Estimate	Lower 95% CI	Upper 95% CI	*P*
PANSS total				
Cannabis	3.20	0.12	6.29	.04
Cannabis × phase	6.42	2.31	10.53	.002
PANSS positive				
Cannabis	2.14	1.41	2.88	<.0001
PANSS negative				
Cannabis	−0.07	−1.11	0.97	.90
Cannabis × phase	2.12	0.75	3.48	.002
Young mania				
Cannabis	0.20	0.15	0.26	<.0001
Calgary depression				
Cannabis	0.05	−0.02	0.11	.16
Cannabis × phase	0.13	0.05	0.21	.002
GAF disability scale				
Cannabis	−1.13	−3.75	1.49	.40
Cannabis × phase	−6.01	−9.32	−2.69	.0004
GAF symptom scale				
Cannabis	−3.27	−6.04	−0.49	.02
Cannabis × phase	−4.87	−8.55	−1.19	.01
GAF total scale				
Cannabis	−1.05	−3.90	1.81	.47
Cannabis × phase	−7.76	−11.42	−4.10	<.0001

Note: GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale. Interactions were only included in the model if they were associated with an improvement of at least 3.84 in the Akaike's Information Criterion value.

also found the use of cannabis to be associated with a younger age of psychosis onset.

We showed that the use of cannabis at either phase of assessment (baseline or 12-month follow-up) was associated with significantly higher scores in PANSS total and positive symptoms, Young Mania and poorer GAF psychosocial functioning- symptoms. While the overall use of cannabis declined over time, we documented considerable variation with some participants (5.9%) initiating cannabis use post-psychosis onset and many (16.8%) continuing to use. There were highly significant cannabis × phase interactions indicating that the continued use of cannabis was associated with significantly greater symptoms for PANSS total scores, PANSS negative, Calgary depression, and GAF psychosocial functioning. These associations were adjusted for age, gender, DUP, age of psychosis onset, ethnicity, and other substance use. Alternatively, we can conclude that cannabis cessation is associated with a substantial benefit.

The results of this study suggest that for PANSS total score for example, the use of cannabis was associated with a 3.2 point increase in symptom severity, whilst the continued use of cannabis was associated with an additional 6.42 point increase in symptom scores. Taken together, this suggests that a person using cannabis at both baseline and 12 months would have a score that was 3.2 points higher at baseline and 9.62 points higher at 1 year. Similarly, for the positive symptoms of psychosis the data suggest that the use of cannabis was associated with a 2.14 point increase in symptom scores, whilst for negative psychotic symptoms the continued use of cannabis was associated with a 2.12 increase in symptom severity.

The increases in scores for the severity of symptoms linked to continued cannabis use represent clinically significant increases in symptomatology. Stable outpatients with psychosis typically have PANSS total scores of between 60 and 80.[36] Therefore, an increase of 9.62 points as found in the current study represents a clinically significant increase in symptomatology, especially in light of suggestions that even subtle symptom elevations as measured by the PANSS are predictive of deterioration.[36]

The relationship between the use of cannabis and the symptoms of mania in FEP has received relatively little attention in the research field: the current study found that cannabis use was associated with a 0.2 point increase in symptom scores for mania. The continued use of cannabis was also associated with a 0.13 point increase in symptom scores for depression.

Previous research examining the impact of cannabis use in psychosis has typically focused only on the effect of cannabis use on psychotic symptoms, but there is also some evidence to suggest that cannabis use may be associated with poorer psychosocial functioning.[9] Here we found continued cannabis use was associated with a 7.76 decrease (ie, worse) total GAF score over the 12 months, suggesting that the continued use of cannabis in FEP may be associated with poorer overall psychosocial functioning.

Overall, our findings suggest that the use of cannabis, and in particular the continued use of cannabis, is associated with poorer symptomatic and functional outcome during the FEP. The mechanism by which cannabis use exacerbates the symptoms of psychosis is not fully understood, although cannabis use may affect the metabolism

and pharmokinetics of antipsychotic medication,[37] and may be associated with reduced medication compliance.[38] Data for this study indicates that prescription of antipsychotic medication was stable over the study period, with 87% of participants at baseline, 88% of participants at 6 months and 81% of participants at 12 months prescribed medication. However, we cannot infer adherence to medication from this data, and it is possible that nonadherence to medication, eg, in those who continue to use cannabis, may have contributed to the results.

Approximately half ($n = 1070$) of all clients approached to take part did not consent; this should be noted as a limitation. Also, similar to other studies,[11,12,18] biochemical verification of substance use was not available in this study, although there is some evidence to suggest that self-report may be reliable, with high concordance to biological assays of drug use.[39] Future research should also consider the frequency of cannabis use and age of cannabis use onset when examining the association between cannabis use and psychotic symptoms. Substance use during the early and prodromal stages of illness has been suggested to mask the onset of psychotic symptoms and delay help seeking for psychosis, resulting in poorer outcome. The potential effect of DUP was controlled for in the main analysis. The current study found a significance level of $P = .055$ for cannabis use and longer DUP, indicating a potential association. It is suggested that this is further explored in future research.

It is possible that the association between the use of cannabis and poorer symptomatic and functional outcome in this study is not the result of symptom exacerbation by cannabis use, but instead results from an attempt at self-medication, in that an increase in psychotic symptoms resulted in the onset or increase in the use of cannabis. However, this seems unlikely given that previous research has found that increases in psychotic symptoms may actually inhibit the use of cannabis[40] and self-report studies have consistently been unable to find any evidence that cannabis use in psychosis is the result of self-medication of psychotic symptoms.[41–43] Clearly, understanding the potential role of cannabis use in psychosis is of paramount importance. It is possible that cannabis may be used in order to alleviate general dysphoria and anxiety rather than the symptoms of psychosis, and further research is needed.

A recent meta-analysis indicates that the cessation of substance use is associated with significant symptomatic improvement in FEP, but this is not the case among patients with more established illness.[44] Previous research has also found a significant effect of continued cannabis use on positive psychotic symptoms[15] and psychotic remission in FEP,[22] although studies have typically suffered from inadequate design, a lack of statistical power and high attrition rates.[20] The current large scale prospective investigation controlled for a range of key confounding factors; the results suggest that the continued use of cannabis may adversely affect a range of symptomatic and functional domains in FEP, and that the magnitude of these effects were clinically significant. These findings highlight the importance of timely intervention for substance use, and cannabis use in particular, during the early stage of psychosis.

This study is the largest prospective cohort study of FEP patients treated routinely within specialized EIS. The results indicate that in spite of this "state of the art" service, the use of cannabis, while declining during the early stage of psychosis, continues to exert a significant impact on symptomatic and functional outcome and accordingly represents a key target for intervention and warrants further evaluation in prospective randomized studies.

Funding

UK Department of Health (RDD/ARF2); National Institute of Health Research (NIHR) under the Programme Grants for Applied Research Programme (RP-PG-0109-10074). M.B. and S.P.S are part funded by the National Institute for Health Research through the Collaborations for Leadership in Applied Health Research and Care for West Midlands (CLAHRC-WM). P.B.J is part funded by the NIHR CLAHRC East of England.

Acknowledgments

M.B. was the CI and grant holder, L.E., P.B.J., D.F., T.A., N.F., V.S., S.P.S., A.C. and M.M. contributed to the study design and execution. The data were analyzed by N.F. and J.S., and with M.B. and A.C. drafted the manuscript. M.B. acts as guarantor. The University of Birmingham (UK) acted as the study sponsor. We thank the Mental Health Research Network for their support and assistance and all National EDEN participants. The views expressed in this publication are those of the authors and not necessarily those of the NHS, NIHR, or the Department of Health. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374:635–645.
2. Birchwood M, Todd J, Jackson C. Early intervention in psychosis: the critical period hypothesis. *Br J Psychiatry*. 1998;172:53–59.
3. Eaton WW, Thara R, Federman B, Melton B, Liang KY. Structure and course of positive and negative symptoms in schizophrenia. *Arch Gen Psychiatry*. 1995;52:127–134.
4. McGlashan TH. Early detection and intervention in schizophrenia: research. *Schizophr Bull*. 1996;22:327–345.
5. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients. *Arch General Psychiatry* 2005;62:975–983.
6. Green B, Young R, Kavanagh D. Cannabis use and misuse prevalence among people with psychosis. *Br J Psychiatry*. 2005;187:306–313.

7. Baeza I, Graell M, Moreno D, et al. Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study). *Schizophr Res*. 2009;113:129–137.
8. Barnett JH, Werners U, Secher SM, et al. Substance use in a population-based clinic sample of people with first-episode psychosis. *Br J Psychiatry*. 2007;190:515–520.
9. González-Pinto A, Alberich S, Barbeito S, et al. Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. *Schizophr Bull*. 2011;37:631–639.
10. Harrison I, Joyce EM, Mutsatsa SH, et al. Naturalistic follow-up of co-morbid substance use in schizophrenia: the West London first-episode study. *Psychol Med*. 2008;38:79–88.
11. Stone JM, Fisher HL, Major B, et al. Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. *Psychol Med*. 2014;44:499–506.
12. Tosato S, Lasalvia A, Bonetto C, et al. The impact of cannabis use on age of onset and clinical characteristics in first-episode psychotic patients. Data from the psychosis Incident cohort outcome study (PICOS). *J Psychiatr Res*. 2013;47:438–444.
13. Yücel M, Bora E, Lubman DI, et al. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. *Schizophr Bull*. 2012;38:316–330.
14. Addington J, Addington D. Patterns, predictors and impact of substance use in early psychosis: a longitudinal study. *Acta Psychiatr Scand*. 2007;115:304–309.
15. Grech A, Van Os J, Jones PB, Lewis SW, Murray RM. Cannabis use and outcome of recent onset psychosis. *Eur Psychiatry*. 2005;20:349–353.
16. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry*. 1994;51:273–279.
17. Hides L, Dawe S, Kavanagh DJ, Young RM. Psychotic symptom and cannabis relapse in recent-onset psychosis. *Br J Psychiatry*. 2006;189:137–143.
18. Clausen L, Hjorthøj CR, Thorup A, et al. 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. *Psychol Med*. 2014;44:117–126.
19. Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis. *Arch Gen Psychiatry*. 2011;68:555–561.
20. Zammit S, Moore TH, Lingford-Hughes A, et al. Effects of cannabis use on outcomes of psychotic disorders: systematic review. *Br J Psychiatry*. 2008;193:357–363.
21. Green AI, Tohen MF, Hamer RM, et al. First-episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res*. 2004;66:125–136.
22. Schimmelmann BG, Conus P, Cotton S, Kupferschmid S, McGorry PD, Lambert M. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. *Eur Psychiatry*. 2012;27:463–469.
23. Bally N, Zullino D, Aubry JM. Cannabis use and first manic episode. *J Affect Disord*. 2014;165:103–108.
24. Birchwood M, Lester H, McCarthy L, et al. The UK national evaluation of the development and impact of Early Intervention Services (the National EDEN studies): study rationale, design and baseline characteristics. *Early Interv Psychiatry*. 2014;8:59–67.
25. Kavanagh D, Saunders J, Young R, Jenner L, Claire A. *A Start Over and Survive Treatment Manual: Evaluation of a Brief Intervention for Substance Abuse in Early Psychosis*. Brisbane, Australia: University of Queensland; 1998.
26. Kavanagh DJ, Trembath M, Shockley N, et al. The DrugCheck Problem List: a new screen for substance use disorders in people with psychosis. *Addict Behav*. 2011;36:927–932.
27. Gossop M, Darke S, Griffiths P, et al. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction*. 1995;90:607–614.
28. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
29. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435.
30. Addington D, Addington J, Maticka-Tyndale E. Specificity of the Calgary Depression Scale for schizophrenics. *Schizophr Res*. 1994;11:239–244.
31. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*. 1976;33:766–771.
32. Jones SH, Thornicroft G, Coffey M, Dunn G. A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). *Br J Psychiatry*. 1995;166:654–659.
33. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*. 1997;53:983–997.
34. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr*. 1974;19:716–723.
35. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med*. 2010;29:2920–2931.
36. Opler LA, Opler MA, Malaspine D. Reducing guesswork in schizophrenia treatment: PANSS can target and gauge therapy, predict outcomes. *Curr Psychiatry*. 2006;5:76–84.
37. Linszen D, Peters B, de Haan L. Cannabis abuse and the course of schizophrenia. In: Castle D, Murray R, eds. *Marijuana and Madness*. Cambridge, MA: Cambridge University Press; 2004:119–126.
38. Turkington A, Mulholland CC, Rushe TM, et al. Impact of persistent substance misuse on 1-year outcome in first-episode psychosis. *Br J Psychiatry*. 2009;195:242–248.
39. Wolford GL, Rosenberg SD, Drake RE, et al. Evaluation of methods for detecting substance use disorder in persons with severe mental illness. *Psychol Addict Behav*. 1999;13:313–326.
40. Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction*. 2005;100:354–366.
41. Fowler IL, Carr VJ, Carter NT, Lewin TJ. Patterns of current and lifetime substance use in schizophrenia. *Schizophr Bull*. 1998;24:443–455.
42. Green B, Kavanagh DJ, Young RM. Reasons for cannabis use in men with and without psychosis. *Drug Alcohol Rev*. 2004;23:445–453.
43. Schaub M, Fanghaenel K, Stohler R. Reasons for cannabis use: patients with schizophrenia versus matched healthy controls. *Aust N Z J Psychiatry*. 2008;42:1060–1065.
44. Mullin K, Gupta P, Compton MT, Nielssen O, Harris A, Large M. Does giving up substance use work for patients with psychosis? A systematic meta-analysis. *Aust N Z J Psychiatry*. 2012;46:826–839.