# Cannabis use is associated with increased psychotic symptoms and poorer psycho-social functioning in first-episode psychosis: A report from the UK National EDEN study

Seddon, J.,[1] Birchwood, M.,[2] Copello, A.,[3] Everard, L.,[4] Jones, P.,[5] Fowler, D.,[6] Amos, T.,[7] Freemantle, N.,[8] Lavis, A.,[9] Singh, S.P.,[2] & Marshall, M.,[10] Sharma, V [11]

[1]National Drug & Alcohol Research Centre, UNSW, 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, UK
[5]Department of Psychiatry, University of Cambridge and CAMEO, Cambridge and Peterborough NHS Foundation Trust, Cambridge, UK
[6]School of Medicine, University of East Anglia, Norwich, 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] School of Health and Population Sciences, University of Birmingham, Birmingham, UK
[10] School of Medicine, University of Manchester, Manchester, UK
[11] Early Intervention service, Cherry Bank Resource Centre, Cheshire and Wirral Partnership NHS Foundation Trust, Ellesmere Port, UK

Corresponding author: Dr J Seddon

## Abstract

Background: 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 psychosis (FEP) and the link with symptomatic course and outcome over one year post psychosis onset.

Method: 1027 FEP patients were recruited upon inception to specialised early intervention services for psychosis in the UK. Participants completed assessments at baseline, six and twelve months.

Results: The results indicate that the use of cannabis was significantly associated with increased severity of psychotic symptoms, mania, depression and poorer psycho-social functioning. Continued use of cannabis following the first episode of psychosis was prognostic of outcome at one year. These associations were significant after adjusting for age, gender, DUP, age of psychosis onset, ethnicity and other drug use.

Conclusion: This is the largest cohort study of first-episode psychosis patients receiving care within early intervention services. Cannabis use, in particular *continued use*, is associated with poorer symptomatic and functional outcome during the first-episode of psychosis. The results highlight the need for effective and early intervention for cannabis use in FEP.



Cannabis use, first-episode psychosis, psychotic symptoms, prospective study

Keywords: Cannabis use, first-episode psychosis, psychotic symptoms, prospective study.

## Introduction

Psychosis is estimated to affect 3.5% of the population over a lifetime (van Os & Kapur, 2009). The early stage, or first-episode of psychosis (FEP) is regarded as a 'critical period', important in determining the long-term outcome of psychosis (Birchwood, Todd & Jackson, 1998). Loss of functioning and social disability occurs during the prodrome in adolescence and during the first two to three years of illness, and plateaus thereafter (McGlashan, 1996; Eaton, Thara, Federman, Melton & Liang, 1995). 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 (Marshall et al., 2005).

There is much unexplained variation in outcome in first-episode psychosis (van Os & Kapur, 2009), therefore a greater need to understand 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 (Green, Young & Kavanagh, 2005), and in FEP the rate of cannabis use has been found to range from 19% to 57% (Baeza et al., 2009; Barnett et al., 2007; Gonzales-Pinto et al., 2011; Harrison et al., 2008; Stone et al., 2014; Tosato et al., 2012). Research in FEP samples suggest that cannabis use may be associated with adverse outcome; such as increased positive symptoms (Addington & Addington, 2007; Grech Van Os, Jones, Lewis & Murray, 2005) and increased rates of psychotic relapse (Hides, Dawe, Kavanagh & Young, 2006), whilst the cessation of cannabis use in FEP has been linked with significant improvements in positive and negative psychotic symptoms, general psychopathology and psycho-social functioning (Baeza et al., 2009; Clausen et al, 2014; González-Pinto et al., 2011; Stone et al., 2014). A recent meta-analysis has also found that cannabis use may be associated with a younger age of psychosis onset (Large, Sharma, Compton, Slade & Nielssen, 2011). However, the majority of studies that have examined the impact of cannabis use have 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 (Zammit et al., 2008). Furthermore, many studies have failed to control for potential confounding factors, such as alcohol and other drug use, which may result in an overestimation of the causal effects of cannabis use in psychosis (Zammit et al., 2008). Well-designed prospective cohort studies involving large clinical samples are needed to definitively determine whether cannabis use affects symptomatic outcome in psychosis.

There is also some evidence which suggests that substance use (AI Green et al., 2004) and cannabis use (Schimmelmann et al., 2012) in FEP may be associated with longer DUP. As DUP is an established prognostic factor for outcome in psychosis (Marshall et al., 2005), this 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 (Bally, Zullino & Aubry, 2014). However, there is little data regarding the impact of cannabis use on mania in FEP.

This paper 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 first-episode psychosis over a period of 12 months after inception to treatment. We examine this

using recent data from the UK National EDEN project, a national, multi-site project that evaluated the effect of early intervention services for people with first-episode psychosis (Birchwood et al., 2014).

It was hypothesised that:

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

## Method

The National EDEN project aimed to evaluate the implementation and impact of Early Intervention Services on young people experiencing first episode of psychosis. The project was conducted within five geographical sites across England (Birmingham, Cambridge, Cornwall, Norwich, and Lancashire). The sample comprised all consecutive referrals from 2005 – 2009. Participants were required to be aged between 14-35 years of age, with a first presentation of psychosis. For full details of the methodology see Birchwood et al. (2014).

### Measures

Participants completed assessments at baseline, six months and twelve months after inception to treatment and substance use was assessed at baseline and 12 months. Assessments were conducted by research assistants who were not directly involved in clinical care.

A complete overview of the assessments used in the National EDEN project is provided in the study protocol (Birchwood et al., 2014). For the purpose of this analysis data in relation to substance use, psychotic symptoms, mania, depression and psycho-social functioning were used.

#### *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 three months as assessed by a revised version of the Kavanagh Drug Check (Kavanagh, Saunders, Young, Jenner & Claire, 1998; Kavanagh et al., 2011). 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?’). The level of dependence was assessed using the Severity of Dependence Scale (Gossop et al., 1995).

#### *Symptom measures*

(i) The Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein & Opler, 1987) was used to assess the severity of positive and negative symptoms of psychosis as well as the level of general psychopathology. The duration of untreated psychosis (DUP) was calculated for all clients upon entry to EIS.
(ii) Mania was assessed using the eleven-item Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler & Mayer, 1978).
(iii) The level of depression was assessed using the nine-item Calgary Depression Scale for Schizophrenia (CDSS; Addington, Addington & Maticka-Tyndale, 1994). The scale has a high degree of specificity and is not confounded by the negative or extrapryramidal symptoms of psychosis.
(iv) Psycho-social functioning was assessed using the Global Assessment of Functioning scale (GAF; Endicott, Spitzer, Fleiss & Cohen, 1976), a clinician rated scale for evaluating the level of psychological, social and occupational functioning on a continuum from 0 – 100. The scale comprises an overall score as well as separate scores for the level of symptoms and disability (the latter two sub-scales are scored along a range of 0-90).

**Data Analysis**

Data were analysed using SPSS 19.0 and SAS 9.3 (SAS Institute, Cary NC).

Chi-square was performed to examine change in the proportion of participants reporting the use of cannabis. Change in the level of 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 and the outcome of interest was estimated using generalised mixed models. In the base model the outcome of interest was the response variable; age, gender, ethnicity, age at psychosis onset, duration of untreated psychosis and other drug 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 using random intercept terms. 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 an improvement of at least 3.84 in the Akaike's Information Criterion value (Akaike, 1974).

## Results

### Participants

1027 participants were recruited upon entry to treatment for first-episode psychosis. 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).

There was a 75.7% (*n* = 777) rate of participant retention at 12 months. There were no significant differences in age [*p* = 0.5], gender [*p* = 0.7], psychiatric diagnosis [*p* = 0.08], or the use of cannabis at baseline [*p* = 0.9] between participants that remained in the study and those lost to follow-up. An additional 1070 clients from early intervention services refused to take part in the study. There were no significant differences in age [*p* = 0.1] or gender [*p* = 0.2] between participants that consented and those that refused to take part.

### Cannabis use over the first 12 months

Sixty-four percent (*n* = 654) of participants reported lifetime use of drugs, with the use of cannabis accounting for most drug use (93%, *n* = 611). 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* = 0.02], and there was a significant association between cannabis use and gender [*p* < 0.001], with cannabis users 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* < 0.001], accompanied by a significant decrease in the mean level of dependence (baseline: 4.38 ± 3.9; 12 months: 3.60 ± 3.8) [*p* = 0.02] and the mean level of drug related problems (baseline: 7.63 ± 5.7; 12 months: 4.70 ± 5.2) [*p* = 0.03] among participants that continued to use cannabis over the 12 month period.

Data regarding the use of cannabis use 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 308.02 days (± 632.89), with a mean age of psychosis onset of 21.33 (± 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* = 0.03], and participants using cannabis at baseline may have a longer duration of DUP (358.9 ± 727.7 days vs. 293.3 ± 600.9 days) [U = 90538.50; *p* = 0.055].

### Cannabis use and psychotic symptoms

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 (see table 1). 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 a 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 drug use.

**Table 1: Cannabis use and symptom severity**

| Model | Estimate | Lower 95% CI | Upper 95% CI | P |
|---|---|---|---|---|
| PANSS Total | | | | |
| Cannabis | 3.20 | 0.12 | 6.29 | 0.04 |
| Cannabis* Phase | 6.42 | 2.31 | 10.53 | 0.002 |
| | | | | |
| PANSS Positive | | | | |
| Cannabis | 2.14 | 1.41 | 2.88 | <.0001 |
| | | | | |
| PANSS Negative | | | | |
| Cannabis | -0.07 | -1.11 | 0.97 | 0.90 |
| Cannabis* Phase | 2.12 | 0.75 | 3.48 | 0.002 |
| | | | | |
| Young Mania | | | | |
| Cannabis | 0.20 | 0.15 | 0.26 | <.0001 |
| | | | | |
| Calgary Depression | | | | |
| Cannabis | 0.05 | -0.02 | 0.11 | 0.16 |
| Cannabis* Phase | 0.13 | 0.05 | 0.21 | 0.002 |
| | | | | |

| | | | | |
|---|---|---|---|---|
| GAF disability Scale | | | | |
| Cannabis | -1.13 | -3.75 | 1.49 | 0.40 |
| Cannabis* Phase | -6.01 | -9.32 | -2.69 | 0.0004 |
| | | | | |
| GAF Symptom Scale | | | | |
| Cannabis | -3.27 | -6.04 | -0.49 | 0.02 |
| Cannabis* Phase | -4.87 | -8.55 | -1.19 | 0.01 |
| | | | | |
| GAF Total Scale | | | | |
| Cannabis | -1.05 | -3.90 | 1.81 | 0.47 |
| Cannabis* Phase | -7.76 | -11.42 | -4.10 | <.0001 |

## Discussion

This is the largest study to examine the link between cannabis use and first episode psychosis. 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 (Large et al., 2011) this study 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 psycho-social functioning- symptoms. While the overall use of cannabis declined over time, we documented considerable variation with some participants (5.9%) initiating cannabis use and many (16.8%) continuing to use. There were highly significant cannabis X 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 psycho-social functioning. These associations were adjusted for age, gender, DUP, age of psychosis onset, ethnicity and other drug use.

The results of this study suggest that for PANSS total 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 (Opler, Opler, & Malaspina, 2006). 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 (Opler et al., 2006).

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 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 psycho-social functioning (González-Pinto et al., 2011). Here we found continued cannabis use was associated with a 7.76 decrease (i.e. worse) total GAF score over the 12 months, suggesting continued cannabis use in FEP may be associated with poorer overall psycho-social 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 first-episode of psychosis. 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 anti-psychotic medication (Linszen, Peters & de Hann, 2004), and may be associated with reduced medication compliance (Turkington et al., 2009). It has also been suggested that substance use during the early and prodromal stages of illness may 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 $p = 0.055$ for cannabis use and longer DUP, indicating a potential association. It is suggested that this is explored in future research.

It is also 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 increases in psychotic symptoms to be associated with decreased cannabis use (Fergusson, Horwood & Ridder, 2005) 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 (Fowler, Carr, Carter & Lewin 1998; Green, Kavanagh & Young, 2004; Schaub, Fanghaenal & Stohler, 2008).

Previous research has found a significant effect of continued cannabis use on positive psychotic symptoms (Grech et al., 2005) and psychotic remission (Schimmelmann et al., 2012), although studies have typically suffered from inadequate design, a lack of statistical power and high attrition rates (Zammit et al., 2008). This large scale prospective investigation suggests that the continued use of cannabis may adversely affect a range of symptomatic and functional domains in FEP, and also illustrates that the magnitude of this effect is clinically significant.

This study is the largest prospective cohort study of first-episode psychosis patients treated routinely within specialised early intervention services. 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 randomised studies.

**Acknowledgements & Authors Contributions**

This work was supported by grants from the UK National Institute of Health Research (NIHR) (2005-2010; 2011-2016). MB was the CI and grant holder, LE, PJ, DF, TA, NF, VS, SS, AL & MM contributed to the study design and execution. The data were analysed by NF and JS, and with MB and AC drafted the manuscript. MB acts as guarantor. We thank the Mental Health Research Network for their support and assistance and all National EDEN participants. We would also like to acknowledge the contribution of Professor Helen Lester in the National EDEN study, who sadly died in March 2013.

Professors Birchwood and Singh are part funded by the National Institute for Health Research (NIHR) through the Collaborations for Leadership in Applied Health Research and Care for West Midlands (CLAHRC-WM). The views expressed in this publication are not necessarily those of the NIHR, the Department of Health, or the University of Warwick.

## References


Addington, J., & Addington, D. (2007). Patterns, predictors and impact of substance use in early psychosis: a longitudinal study. *Acta Psychiatrica Scandinavica, 115*, 304- 309.

Addington, D., Addington, J., Maticka-Tyndale, E. (1994) Specificity of the Calgary Depression Scale for schizophrenia. *Schizophrenia Research, 11*, 239-244.

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control, 19*: 716-23.

Baeza, I., Graell, M., Moreno, D., Castro-Fornieles, J., Parellada, M., González-Pinto, A.,... & Arango, C. (2009). Cannabis use in children and adolescents with first episode psychosis: Influence on psychopathology and short-term outcome (CAFEPS study). *Schizophrenia Research, 113*, 129-137.

Bally, N., Zullino, D., & Aubrey, J. M. (2014). Cannabis use and first manic episode. *Journal of Affective Disorders, 165,* 103-108.

Barnett, J. H., Werners, U., Secher, S. M., Hill, K. E., Brazil, R., Masson, K.,... & Jones, P. B. (2007). Substance use in a population-based clinic sample of people with first-episode psychosis. *British Journal of Psychiatry, 190*, 515-520.

Birchwood, M., Lester, H., McCarthy, L., Jones, P., Fowler, D., Amos.,… Marshall, M. (2014). The UK national evaluation of the development and impact of Early Intervention Services (the National EDEN studies): study rationale, design and baseline characteristics. *Early Intervention in Psychiatry, 8*, 59-67.

Birchwood, M., Todd, J., & Jackson, C. (1998). Early intervention in psychosis; The critical period hypothesis. *The British Journal of Psychiatry, 172*(33), 53-59.

Clausen, L., Hjorthøj, C. R., Thorup, A., Jeppesen, P., Petersen, L., Bertelsen, M., & Nordentoft, M. (2014). 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. *Psychological Medicine, 44*, 117-126.

Eaton, W. W., Thara, R., Federman, B., Melton, B., & Liang, K. (1995). Structure and course of positive and negative symptoms in schizophrenia. *Archives of General Psychiatry, 52*, 127-134.

Endicott, J., Spitzer, R. L., Fleiss, J. L. & Cohen, J. (1976). The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry, 33*(6), 766-771.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2005). Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction, 100*, 354-366.

Green A. I., Tohen M. F., Hamer R. M., Strakowski S. M., Lieberman J. A., Glick I., & Clark W. S. (2004). First-episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophrenia Research 66,* 125–136.

Green, B., Kavanagh, D. J., & Young, R. (2004). Reasons for cannabis use in men with and without psychosis. *Drug and Alcohol Review, 23,* 445-453.

Green, B., Young, R., & Kavanagh, D. (2005). Cannabis use and misuse prevalence among people with psychosis. *British Journal of Psychiatry, 187,* 306-313.

Grech, A., Van Os, J., Jones, P. B., Lewis, S. W., & Murray, R. M. (2005). Cannabis use and outcome of recent onset psychosis. *European Psychiatry, 20*, 349-353.

González-Pinto, A., Alberih, S., Barbeito, S., Gutierrez, M., Vega, P., Ibánez, B.,... & Arango, C. (2011). Cannabis and First-Episode Psychosis: Different long-term outcomes depending on continued or discontinued use. *Schizophrenia Bulletin, 37* (3), 631-639.

Gossop, M., Darke, S., Griffiths, P., Hando, J., Powis, B., Hall, W., & Strang, J. (1995). The Severity of Dependence Scale (SDS): Psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction, 90,* 607-614.

Harrison, I., Joyce, E. M., Mutsatsa, S. H., Hutton, S. B., Huddy, V., Kapasi, M., Barnes, T. R. E. (2008). Naturalistic follow-up of co-morbid substance use in schizophrenia: the West London first-episode study. *Psychological Medicine, 38*, 79-88.

Hides, L., Dawe, S., Kavanagh, D.J., & Young, R.M. (2006). Psychotic symptom and cannabis relapse in recent-onset psychosis. *British Journal of Psychiatry, 189,* 137-143.

Kavanagh, D., Saunders, J., Young, R, Jenner, L., & Claire, A. (1998). *A start over and survive treatment manual: Evaluation of a brief intervention for substance abuse in early psychosis.* Brisbane, Australia: University of Queensland. - 213 -

Kavanagh, D. J., Trembath, M., Shockley, N., Connolly, J., White, A., Isailovic, A.,... & Connor, J. (2011). The DrugCheck Problem List: A new screen for substance use disorders in people with psychosis. *Addictive Behaviors, 36*, 927- 932.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13,* 261-276.

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis. *Arch Gen Psychiatry, 68,* (6), 555-561

Linszen, D., Peters, B., & de Haan, L. (2004). Cannabis abuse and the course of schizophrenia. In Castle, D., & Murray, R. (EDs). *Marijuana and Madness* (pp. 119-126). Cambridge; Cambridge University Press.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients. *Arch General Psychiatry, 62,* 975-983.

McGlashan, T. H. (1996). Early detection and intervention in schizophrenia: Research. *Schizophrenia Bulletin, 22*, 327-345.

Schaub, M., Fanghaenel, K., & Stohler, R. (2008). Reasons for cannabis use: patients with schizophrenia versus matched healthy controls. *Australian and New Zealand Journal of Psychiatry, 42,* 1060-1065.

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

Stone, J. M. Fisher, H. L., Major, B., Chisholm, B., Woolley, J., Lawrence, J.,…Young, A. H. (2014). Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. *Psychological Medicine, 44*, 499-506.

Tosato, S., Lasalvia, A., Bonetto, C., Mazzoncini, R., Cristofalo, D., De Santi, K.,… Ruggeri, M. (2013). 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). *Journal of Psychiatric Research, 47*, 438-444.

Turkington, A., Mulholland, C. C., Rushe, T. M., Anderson, R., McCaul, R., Barrett, S. L.,... & Cooper, S. J. (2009). Impact of persistent substance misuse on 1-year outcome in first episode psychosis. *The British Journal of Psychiatry, 195*, 242-248.

Opler, L. A., Opler, M. A., & Malaspine, D. (2006). Reducing guesswork in schizophrenia treatment: PANSS can target and gauge therapy, predict outcomes. *Current Psychiatry, 5*, 76-84.

Van Os, L., & Kapur, S. (2009). Schizophrenia. *Lancet, 374*, 635–45.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D.A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry, 133*, 429-435.

Zammit, S., Moore, T. H. M. Lingford-Hughes, A., Barnes, T. R. E., Jones, P. B., Burke, M., & Lewis, G. (2008). Effects of cannabis use on outcomes of psychotic disorders: systematic review. *The British Journal of Psychiatry, 193*, 357-363.