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A prospective study of cannabis use as a risk factor for non-adherence and treatment dropout in first-episode schizophrenia

Rachel Miller^{a,i,*}, Geoffrey Ream^b, Joanne McCormack^a, Handan Gunduz-Bruce^{a,ii}, Serge Sevy^a, and Delbert Robinson^a

^aZucker Hillside Hospital, Glen Oaks, NY, 11004, United States

^bAdelphi University, 1 South Avenue, Garden City, NY 11530, United States

Abstract

Introduction—Although several studies have reported on cannabis use and adherence for first episode of psychosis patients, the findings remain unclear as to whether cannabis use is a risk factor for poor adherence in young people with first-episode schizophrenia. This study was designed to follow patients' use of cannabis and adherence in a naturalistic setting during the first 12 months of treatment. It examines whether cannabis use is a risk factor for two distinct types of non-adherence: non-adherence to medication and treatment dropout..

Methods—Participants were 112 first-episode schizophrenia patients of diverse backgrounds at two community hospitals, enrolled in of two second-generation antipsychotic medications. a study of differential effectiveness Multiple indicators were used to assess cannabis use and adherence to medication. Patients were encouraged to continue in the study even after periods of treatment refusal or change from study to standardized medication. Study hypotheses were tested using Cox proportional hazards models with cannabis use as a time-varying covariate.

Results—After 12 months, 23 had dropped out and 37 had at some point been non-adherent to medication. Of 34 participants who used cannabis during treatment, 32 had a prior diagnosis of

*Corresponding author. National Institute of Mental Health, 10 Center Drive, Bldg. 10, Room 3B24, Bethesda, MD 20892-1600, United States. Tel.: 301 496-7962; Fax: 301 402-0296; E-mail address: mrachel@mail.nih.gov.

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ⁱPermanent addresses: National Institute of Mental Health, 10 Center Dr., Bldg. 10, Bethesda, MD 20892-1600, United States

ⁱⁱYale University School of Medicine, 300 George St., New Haven CT 06511, United States

Geoffrey Ream, E-mail: ream@adelphi.edu Joanne McCormack, E-mail: JMcCorma@lij.edu Serge Sevy, E-mail: ssevy@lij.edu Handan Gunduz-Bruce, E-mail: hg68@email.med.yale.edu Delbert Robinson, E-mail address: Robinson@lij.edu

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cannabis abuse/dependence and 30 were male. Independently of age, race, socioeconomic status, gender, site, and medication assignment, cannabis use significantly increased hazard of non-adherence by a factor of 2.4 ($p < .001$) and hazard of dropout by a factor of 6.4 ($p = .034$).

Conclusion—Results indicate that cannabis use is a risk factor for non-adherence to medication and dropout from treatment. Treatment for first-episode schizophrenia may be more effective if providers address the issue of cannabis use with patients throughout the early years of treatment, especially for those with existing cannabis abuse/dependence.

Keywords

Schizophrenia; adherence; dropout; cannabis; first-episode; substance abuse; compliance

1. Introduction

Despite the promise of improving outcome with early treatment of first-episode of schizophrenia (Birchwood et al., 1998; Bottlender et al., 2002; Larsen et al., 1998), relapse of psychosis often occurs due to medication discontinuation (Novak-Grubic and Tavcar, 2002; Robinson et al., 1999; Svedberg et al., 2001). Rates of non-adherence to antipsychotic medications are generally put at 50% (Lacro et al., 2002) and possibly higher for first-episode patients (Coldham et al., 2002; Mojtabai et al., 2002). Rates of treatment dropout, the ultimate form of non-adherence, is less often reported upon, and range between 20% to 56.5% (Gaebel et al., 2002; Kamali et al., 2006; Linden et al., 2001; Novak-Grubic and Tavcar). Dropout is an important variant of non-adherence because it prevents patients from having professionals who can restart treatment as soon as symptoms begin to return.

There have been conflicting reports regarding cannabis, the primary substance of use for first-episode schizophrenia (FES) patients (Buhler et al., 2002; Van Mastrigt et al., 2004), and non-adherence to medication or treatment dropout. Addington and Addington (2001) found no difference in dropout rates for participants in the Calgary Early Psychosis Program for cannabis versus non cannabis using participants. In that same program, however, cannabis use was identified as a risk factor for non-adherence in patients with schizophrenia and schizophrenia spectrum disorders (Coldham et al., 2002). Coldham et al. used data collected at 3 time points; measured adherence retrospectively by chart review, case manager report and consensus; and measured cannabis use with Case Manager Rating Scale for Substance Use Disorder (Drake et al., 1990). Perkins et al. (2006) utilized self-report in first episode psychosis patients for cannabis use assessment and pill counts for adherence assessment and found no association with adherence. In his seminal study of cannabis use and FES, Linszen et al. (1994) also found no differences for adherence in cannabis using and non-using groups. Findings also are mixed in studies that group cannabis with other substances. Verdoux et al. (2000), who included all patients with psychosis and grouped cannabis under the category of “Other,” found a non-significant association between cannabis use and medication adherence, as did Mutsatsa et al. (2003). However, in a prospective study of adherence in FES using the Compliance Interview, Kamali et al. (2006), reported “substance misuse” predicted non-adherence. Several factors that may affect study outcomes include lack of diagnostic specificity (i.e., including first-episode psychosis along with first-episode schizophrenia patients); grouping cannabis with other substances; and varying methods of measurement such as retrospective data gathering and the use of single measures (i.e., self-report or pill counts) rather than multiple measures to better capture these variables. Furthermore, it is very difficult to follow patients who leave treatment, as noted by Kamali et al. (2006), who report that 40% of their patients did not participate in follow-up.

This study seeks to improve our understanding of the relationship between cannabis use and two distinct forms of adherence problems: poor medication adherence and treatment dropout. We increase diagnostic specificity by including only participants with schizophrenia, schizoaffective disorder and schizophreniform disorder and improve measurements of both cannabis use and adherence by using multiple methods of assessment. Further, by encouraging patients to return to the study after periods of non-adherence or substance use, as is often the case in non-research treatment programs, we endeavor to maximize the time in the study, thereby capturing data that is not usually available in controlled trials of medication treatment. In addition, the cohort being studied is diverse for both socioeconomic status, a factor that may affect adherence for young people (Wamala et al., 2007), and ethnicity, recognized to play a role in antipsychotic medication adherence (Opolka, J. et al., 2003), both variables for which little has been reported in the context of cannabis use and adherence for FES patients. We hypothesize that cannabis use increases the hazard of a patient becoming non-adherent to a medication regimen and also increases the hazard of a patient dropping out of treatment. We expect these relationships will remain significant even after controlling for correlates of age, race, gender, site, medication assignment, and socioeconomic status.

2. Method

2.1 Subjects

Subjects were enrolled in the Preventing Morbidity in First Episode Schizophrenia Study, a prospective longitudinal study (1998 to 2007) of FES patients designed to compare the effectiveness of two atypical antipsychotic medications, olanzapine and risperidone (Robinson et al., 2006). Patients were recruited at two New York not-for-profit hospitals, one in Queens serving low to middle-class residents, and the other in the Bronx serving predominantly poor minority residents. All subjects received psychoeducation, family, and individual treatments. Treatment at the Queens hospital also included group treatment for all patients with particular focus on problems of adherence, substance (primarily cannabis) use, and insight (Miller et al., 2005).

The study recruited participants between 16 and 40 years of age presenting for treatment for the first time with recent-onset schizophrenia in both inpatient and outpatient venues. Patients were treated as hospital inpatients if necessary and then followed in outpatient treatment. Patients had a complete baseline psychiatric evaluation at the time of enrollment. They were eligible for the study if they had a diagnosis of schizophrenia, schizophreniform or schizoaffective disorder as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; version 2.0, 8/98; First et al., 1998), and were competent to sign informed consent. Patients were excluded if symptoms were deemed to be primarily substance-induced, if they had recent intravenous drug use, more than 12 weeks of previous antipsychotic treatment, any serious medical condition, significant risk of suicidal or homicidal behavior, or cognitive or language limitations. The study's protocol was approved by both hospitals' Institutional Review Boards, and Adelphi University's Institutional Review Board approved secondary analysis of the data. Informed consent was provided by all subjects and, if available, by a family member.

2.2 Measures

Based on our previous experience, we recognized that FES patients often miss sessions and are not always attentive to rating schedules. Since this study sought to follow patients over a long period of time in order to capture the long term outcomes of medication randomization, patients were not dropped from the study if they did not come in for weekly treatment or ratings, and patients were accepted back into the study if they made the decision to return after an extended period of time.

2.2.1 Cannabis use—Information on cannabis use came from five different sources: (1) once-monthly administration of the SADS C+PD (Spitzer & Endicott., 1978) with additional questions regarding substance use; (2) the substance use disorders sections of the Structured Clinical Interview for DSM-IV for Axis I Disorders (SCID; First et al., 1998) administered every six months; (3) urine toxicology; (4) clinician reports; and (5) family reports. Consensus decisions based on all these sources were made at weekly team meetings and recorded. Patients who were discontinued from their assigned study medication were followed less closely by SADS C+PD interviews but all other sources were maintained. Because we could be confident about whether they had used cannabis but not about how much, how often, why, or to what effect, cannabis use is operationalized here as a simple dichotomous indicator. Our data include one rating for each month after month zero.

2.2.2 Dropout—A participant was considered as dropping out of treatment if he or she left treatment for more than one month and was not following up with treatment elsewhere (Robinson et al., 2002). Patients were not considered dropouts if they returned to the study.

2.2.3 Adherence—Adherence data were collected in weekly team meetings based on all available data including participant, family and clinician report. Additionally, plasma levels of antipsychotic medication were tested at week 16, 24, 36, and 52. Additional blood tests were performed if adherence was questionable. Plasma levels were not sensitive to the dose of antipsychotic medication being taken, only whether the participant had any antipsychotic medication or none at all. Final scores were assigned by the research rater based on all the data available. The weekly measures were averaged over one month to provide a positive or negative measure: < 50% adherence is non-adherent; $\geq 50\%$ adherence is adherent. Although there is no consensus on what is considered good adherence, medication adherence is often categorized as poor when medication is discontinued against the physician's advice (Verdoux et al., 2000) and is frequently irregular at 25% to 49% (Garavan et al., 1998). In this study, we did not assume dropouts were non-adherent; we only coded them as non-adherent if it was known that they had stopped taking medication.

2.2.4 Demographic and other controls—Data for this study include indicators of whether the patient was at the Queens or Bronx site and whether the patient's initial medication assignment was risperidone or olanzapine. Our data also include age, race, gender, and socioeconomic status. Racial categories included White, Black, Latino, Asian, and "Other" races. SES is measured with the Hollingshead's and Redlich Index of Social Position (Hollingshead and Redlich, 1958), a combination of information on education and occupational prestige.

2.3 Statistical Analyses

Analyses for this study were completed using STATA 9.0/SE. Bivariate tests were conducted using standard commands for t-test and chi-square. Survey or other robust estimation procedures were not employed. Study hypotheses were tested using Cox proportional hazard models, which were preferred because of the Cox model's robustness against missing data (allowing participants to be accounted for even if they left the study and came back) and lack of distributional assumptions for the hazard function. Within the Cox models, "exposure" to "risk" of dropout and non-adherence are assumed to begin at month 0, when observations begin. Observations for cannabis use, adherence, and dropout end either at the last month for which there was valid data for the participant or are right-censored at 12 months. Cannabis use, adherence, and dropout are the only time-varying variables; all other study variables are time-invariant. In order to establish non-spuriousness of the findings, control variables of age, race, SES, sex, medication assignment, and site were also entered into the multivariate models as covariates.

3. Results

3.1 Descriptive Findings

Table 1 describes the demographic characteristics of the sample. There was an almost-significant sex difference in age, with males' mean age at 23 and females' at 25, $t(110) = -1.8$, $p = .082$. The sex difference in mean SES — 58 for males and 52 for females — was statistically significant, $t(108) = 2.4$, $p = .018$. Diagnoses were as follows: 84 schizophrenia, 19 schizophreniform disorder, and 9 schizoaffective disorder. One male and one female were missing data on SES; predicted values for SES from a multiple regression model containing race, age, and gender were imputed for them. There was also a gender difference in prior cannabis abuse/dependence diagnosis, with 55% of the males (that is, the males with valid values, 1 was listed as “unknown”) and 27% of the females reporting this, $\chi^2(1df, n = 111) = 7.5$, $p = .006$. Importantly, 34 participants used cannabis at some point during treatment, and all but 2 of them had a prior diagnosis of cannabis abuse/dependence.

Proportion using cannabis hovered between 15% and 20% for most of the study period. The proportion of participants adherent to medication started at 95% at the beginning of the study and declined steadily to 81%. Despite enormous efforts made to collect data within the rating schedule, missing data were a persistent problem. Over the 12 months of data collection, assuming that all participants who were not dropouts were still in the study, an average of 13% and as many as 22% of participants were missing data for cannabis use and an average of 19% and as many as 35% of participants were missing data for adherence.

3.2 Cannabis Use and Hazard of Non-Adherence and Drop-Out from Treatment

Figures 1 and 2 depict the Nelson-Aalen estimates of the cumulative hazard of dropout and non-adherence, respectively, as a function of cannabis use without adjusting for controls. Table 2 reports results of Cox proportional hazards models testing the hypothesis that cannabis use, as a time-varying covariate, is a risk factor for non-adherence to medication and dropout from treatment controlling for time-invariant covariates of age, sex, race, SES, medication assignment, and site. Asians had to be excluded from the analysis of non-adherence because all were adherent during months for which they had valid data for cannabis use. Cannabis use was found to increase the hazard of dropout from treatment by a factor of 6.4 and the hazard of non-adherence by a factor of 2.4.

When the same analysis predicting non-adherence was run with only participants that had a prior cannabis abuse/dependence diagnosis, the hazard ratio increased to 4.7, $p < .001$, and a significant effect for age emerged, $HR = 0.86$, $p = .042$. When these analyses are run without cannabis use in the model, significant effects for gender emerge, $HR = 0.31$, $p < .001$ among all participants, $HR = 0.12$, $p = .040$, for participants with prior cannabis abuse/dependence diagnosis. Note that in the analyses reported in Table 2, however, there is no significant effect for gender. Male gender, therefore, can be said to be a significant risk factor for cannabis abuse/dependence and cannabis use, and this association explains males' greater hazard of non-adherence to medication. Similar explorations could not be made with dropout as the dependent variable because the low number of dropouts left insufficient statistical power for analyses.

Fifteen participants had current diagnoses of anxiety or mood disorders, with Bipolar NOS, depressive disorders, Obsessive-Compulsive Disorder, and phobias (either specific phobias or social phobia) occurring in roughly equal proportions. There were an additional five cases diagnosed with anxiety or mood disorders in the past which had remediated before they began their current treatment for schizophrenia and three cases in which the anxiety or mood disorder began after the schizophrenia. Presence of a current anxiety or mood disorder diagnosis was not associated with medication assignment, site, race, age, or (according to Cox regression

analyses with current diagnosis as the only independent variable) hazard of cannabis use during treatment, non-adherence, or dropout. There was a significant difference by sex, with 18% of male and 3% of female participants reporting a prior diagnosis with an anxiety or mood disorder, $\chi^2(1, n = 112) = 4.6, p = .032$.

4. Discussion

The results of this study indicate that, for FES patients, cannabis use increases hazard of both non-adherence to antipsychotic medication regimen for schizophrenia and dropout of treatment. Our finding that 44% of FES patients coming into treatment for the first time have a cannabis abuse/dependence diagnosis are on the upper end of recent reports (Green et al., 2004; Hambrecht and Hafner, 2000; Larsen et al., 2006; Linszen et al., 1994; Wade, 2006). This is not surprising, given that participants came from diverse neighborhoods, including densely populated metropolitan areas of New York. Although differing from Linszen et al., our adherence findings are consistent with other studies of substance abuse and adherence for people with schizophrenia (Lacro et al., 2002) and first-episode psychosis (Coldham et al., 2002). These findings are also consistent with what the authors have observed clinically about how psychiatric symptoms, addictive disorders, and environmental factors contribute to each other over time to jeopardize treatment adherence. Psychotic symptoms make it very difficult for those who already have a cannabis abuse problem to utilize the judgment and restraint required to avoid cannabis. Once people are using cannabis again, there is a further decline in judgment and impulse control as well as an increase in psychosis, a decline in insight, and decreased motivation or ability to maintain treatment regimens. It will be the task of future research to further investigate this reciprocal effect and evaluate efforts to address it in treatment.

Of particular relevance is the finding that many FES patients return to cannabis use early in treatment, a behavior which may lead to a cycle of poor adherence and relapse. Moreover, the vast majority of participants who used cannabis during treatment (32 of 34) had an existing diagnosis of cannabis abuse/dependence. This is important for understanding possible causal relationships between cannabis use and non-adherence; i.e., although the Cox regression models in this study arguably leave open the possibility that non-adherence and dropout may lead to or co-occur with cannabis use among patients with an existing diagnosis of cannabis abuse/dependence, non-adherence is clearly not driving large numbers of patients without that diagnosis to start using cannabis. The vast majority of participants with an existing diagnosis of cannabis abuse/dependence were male (40 of 49). In the context of what is known about cannabis practices in the New York City area, this gender difference may have to do with males' greater predilection for cannabis use practices that entail special risk of abuse/dependence, e.g., smoking while alone and combining marijuana with tobacco, both by smoking blunts (marijuana rolled into cigar shells) and "chasing" marijuana with tobacco (Ream et al., 2008). Males' preference for these practices may be because males experience a stronger interaction effect between tobacco and marijuana than females do (Penetar et al., 2005).

The significant finding that the patients at the Bronx site were at greater risk for non-adherence is important to note. It may be that the population at this site has fewer support systems available to help patients stay adherent, that there was a difference between the two populations that may require additional study, or that the Queens patients had more formal interventions around substance use and adherence than the Bronx patients. Because this study's multivariate models controlled for differences in site and cannabis use was found to be a significant predictor after controlling for site, it is possible to be confident that differences between sites did not cause the differences that this study's models attribute to cannabis use.

4.1 Study Strengths and Limitations

This study has several strengths, particularly the ethnic and socioeconomic diversity of the cohort, the use of multiple indicators to ascertain adherence and cannabis use in a prospective manner, and its having followed a large number of subjects for a one-year period despite the inclination of first-episode patients to leave treatment for periods of time. Further, the study included only patients with a clear diagnosis of schizophrenia, schizoaffective and schizophreniform disorder, excluding patients whose psychosis may be of short duration, caused by substances, or whose diagnosis was later revised as an affective disorder. Another advantage of our methods is that it considers dropout of treatment and non-adherence to medication as two separate outcomes, an important differentiation for the field since non-adherence may be lessened with treatment while dropout leaves the patient likely to return for help only when the situation is critical.

A weakness is that study participants were enrolled in a medication research study and therefore may not be representative of people experiencing a first episode of schizophrenia who are unwilling or unable to participate in such a study. Although we tried to include a comprehensive set of controls, there might be factors we did not measure that would predict both cannabis use and non-adherence to treatment among this population. Further, since cannabis was the primary substance used by subjects, we cannot determine the role other substances may have in adherence/drop-out.

5. Conclusion

For FES patients who are in the beginning process of treatment, both poor medication adherence and dropout present significant treatment problems ranging from relapse and its sequelae to loss of opportunity to optimize early treatment strategies. Dropping out of treatment, the most serious form of adherence failure, requires special attention since patients without care may be at greater risk for dangerous behaviors. The particular risk of cannabis use during treatment among patients with a prior diagnosis of cannabis abuse/dependence is one of the striking findings of this study. All of the patients in this study received on-going psychoeducation regarding the use of substances, especially cannabis, as well as treatment to enhance adherence. This treatment focus may have been helpful in preventing non-users from beginning to use cannabis given that only one patient with no prior use tried cannabis for the first time during the 12- months, a finding similar to that of Wade et al. (2006), who found only 2 patients in their study of first-episode psychosis in Australia commencing substance use during the first 15 months of treatment. Nevertheless, of the 49 patients with a cannabis abuse/dependence diagnosis at first presentation, 32 of them returned to cannabis use during the first year of treatment despite psychoeducation and their experience of psychotic symptoms. This points to the need for developing treatment targeted to address the common co-occurrence of cannabis use, non-adherence to treatment, and symptoms of schizophrenia for FES patients (Addington and Addington, 2001; Linszen et al., 2001; Miller et al., 2005). Such treatment will need to attend to the fact that cannabis abuse/dependence is a long-term problem and that relapse of cannabis use can significantly interfere with treatment.

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References

- Addington J, Addington D. Impact of an early psychosis program on substance use. *Psychiatr Rehabil J* 2001;25(1):60–67. [PubMed: 11529454]
- Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry* 1998;172(33):53–59. [PubMed: 9534833]
- Bottlender R, Sato T, Jager M, Groll C, Strauss A, Moller HJ. The impact of duration of untreated psychosis and premorbid functioning on outcome of first inpatient treatment in schizophrenia and schizoaffective patients. *Eur Arch Psychiatry Clin Neurosci* 2002;252:226–31. [PubMed: 12451464]
- Buhler B, Hambrecht M, Loffler W, Heiden W, Hafner H. Precipitation and determination of the onset and course of schizophrenia by substance abuse—a retrospective and prospective study of 232 population-based first illness episodes. *Schizophr Res* 2002;54:243–51. [PubMed: 11950549]
- Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatr Scand* 2002;106:286–90. [PubMed: 12225495]
- Drake RE, Osher FC, Noordsy DL, Teague GB, Hurlbut SC, Beaudett MS. Diagnosis of alcohol use disorders in schizophrenia. *Schizophr Bull* 1990;16:57–67. [PubMed: 2333482]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition. Biometrics Research Department; New York: 1998. SCID-I/P, Version 2.0, 8/98 revision
- Gaebel W, Janner M, Frommana N, Pietzcker A, Kopcke W, Linden M, et al. First vs multiple episode schizophrenia: Two-year outcome of intermittent and maintenance medication strategies. *Schizophr Res* 2002;53:145–59. [PubMed: 11728846]
- Garavan J, Browne S, Gervin M, Lane A, Larkin C, O’Callaghan E. Compliance with neuroleptic medication in outpatients with schizophrenia: Relationship to subjective response to neuroleptics; attitudes to medication and insight. *Compr Psychiatry* 1998;39(4):215–19. [PubMed: 9675506]
- Green AI, Tohen MF, Hamer RM, Strakowski SM, Lieberman JA, Glick, et al. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res* 2004;66:125–35. [PubMed: 15061244]
- Hambrecht M, Hafner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *Aust N Z J Psychiatry* 2000;34(3):468–75. [PubMed: 10881971]
- Hollingshead, AB.; Reidlich, FC. Social class and mental illness: A community study. Wiley; New York: 1958.
- Kamali M, Kelly BD, Clark M, Browne S, Gervin M, Kinsella A, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. *Eur Psychiatr* 2006;21:29–33.
- Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of recent literature. *J Clin Psychiatry* 2002;63:892–909. [PubMed: 12416599]
- Larsen TK, Johannessen JO, Opjordsmoen S. First-episode schizophrenia with long duration of untreated psychosis. Pathways to care. *Br J Psychiatry* 1998;172:45–52.
- Larsen TK, Melle I, Auestad B, Friis S, Haahr U, Johannessen JO, et al. Substance abuse in first-episode non-affective psychosis. *Schizophr Res* 2006;88:55–62. [PubMed: 16971092]
- Linden M, Godemann F, Gaebel W, Kopke W, Muller P, Muller-Spahn F, et al. A prospective study of factors influencing adherence to a continuous neuroleptic treatment program in schizophrenia patients during 2 years. *Schizophr Bull* 2001;27(4):585–96. [PubMed: 11824485]
- Linszen DH, Dingemans PM, Lenior ME. Early intervention and a five year follow up in young adults with a short duration of untreated psychosis: Ethical implications. *Schizophr Res* 2001;51:55–61. [PubMed: 11479066]
- Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* 1994;51:273–79. [PubMed: 8161287]

- Miller R, Caponi J, McCormack, Sevy S, Robinson D. The insight-adherence-abstinence triad: An integrated treatment focus for cannabis-using first-episode schizophrenia patients. *Bull Menninger Clin* 2005;69:220–36. [PubMed: 16178711]
- Mojtabai R, Lavelle J, Gibson PJ, Sohler NL, Craig TJ, Carlson GA, et al. Gaps in use of antipsychotics after discharge by first-admission patients with schizophrenia, 1989 to 1996. *Psychiatr Serv* 2002;53(3):337–39. [PubMed: 11875230]
- Mutsatsa SH, Joyce EM, Hutton SB, Webb E, Gibbins H, Paul S, et al. Clinical correlates of early medication adherence: West London first episode schizophrenia study. *Acta Psychiatr Scand* 2003;108:439–46. [PubMed: 14616225]
- Novak-Grubic V, Tavcar R. Predictors of noncompliance in males with first-episode schizophrenia, schizophreniform and schizoaffective disorder. *Eur Psychiatr* 2002;17(3):148–54.
- Opolka JL, Rascati KL, Brown CM, Gibson PJ. Role of ethnicity in predicting antipsychotic medication adherence. *The Annals of Pharmacotherapy* 2003;37:625–630. [PubMed: 12708934]
- Penetar DM, Kouri EM, Gross MM, McCarthy EM, Rhee CK, Peters EN, et al. Transdermal nicotine alters some of marihuana's effects in male and female volunteers. *Drug Alcohol Depend* 2005;79(2):211–223. [PubMed: 16002030]
- Perkins DO, Johnson JL, Hamer RM, Zipursky RB, Keefe RS, Centorrino F, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. *Schizophr Re* 2006;83:53–63.
- Ream GL, Benoit E, Johnson BD, Dunlap E. Smoking tobacco along with marijuana increases symptoms of cannabis dependence. *Drug Alcohol Depend* 2008;95:199–208. [PubMed: 18339491]
- Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Re* 2002;57:209–19.
- Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 1999;156:544–49. [PubMed: 10200732]
- Robinson DG, Woerner MG, Napolitano B, Patel RC, Sevy SM, Gunduz-Bruce H, et al. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *Am J Psychiatry* 2006;163:2096–102. [PubMed: 17151160]
- Spitzer, RL.; Endicott, J. *Schedule for Affective Disorders and Schizophrenia—Change Version*. Vol. 3rd ed. New York State Psychiatric Institute; 1978.
- Svedberg B, Mesterton A, Cullberg. First-episode non-affective psychosis in a total urban population: a 5-year follow-up. *Soc Psychiatr Psychiatri Epidemiol* 2001;36(7):322–37.
- Van Mastrigt S, Addington J, Addington D. Substance misuse at presentation to an early psychosis program. *Soc Psychiatr Psychiatri Epidemiol* 2004;39:69–72.
- Verdoux H, Lengronne J, Liraud F, Gonzales B, Assens F, Abalan F, et al. Medication adherence in psychosis: Predictors and impact on outcome. A 2-year follow-up of first-admitted subjects. *Acta Psychiatr Scand* 2000;102:203–10. [PubMed: 11008856]
- Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Course of substance misuse and daily tobacco use in first-episode psychosis. *Schizophr Re* 2006;81:145–150.
- Wamala S, Merlo J, Bostrom G, Hogstedt C, Agren G. Socioeconomic disadvantage and primary non-adherence with medication in Sweden. *Int J Quality Health Care* 2007;19:134–140.

Figure 1.

Nelson-Aalen estimated cumulative hazard of dropout as a function of cannabis use.

Figure 2.
Nelson-Aalen estimated cumulative hazard of non-adherence as a function of cannabis use.

Table 1

Description of Sample

Gender	n	Race	n
Male	78	White	22
Female	34	Black	60
		Latino	15
Site	n	Asian	7
Hillside	80	Other	8
Bronx	32		
Medication	n	Cannabis abuse/ dependence diagnosis	
Olanzapine	55	No	63
Risperidone	56	Yes	49
		SES	Age
Minimum	22		16
25th %ile	44		20
50th %ile	58		22
75th %ile	66		26
Maximum	80		38
Months in Treatment	% Using Cannabis	% Adherent to Medication	# Drop- out
1	6%	95%	8
2	13%	94%	1
3	18%	89%	0
4	14%	90%	3
5	17%	86%	4
6	18%	84%	1
7	16%	82%	0
8	18%	84%	1
9	15%	82%	0
10	16%	80%	1
11	17%	80%	0

Months in Treatment	% Using Cannabis	% Adherent to Medication	# Drop-out
12	22%	81%	4

Table 2

Cox Proportional Hazards Models Predicting Dropout from Cannabis Use and non-Adherence to Medication, Controlling for Medication, Site, Race, Sex, Age, and SES

	Dropout		Non-Adherence	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Cannabis Use	6.4 [*]	[1.2, 35.6]	2.4 ^{***}	[1.5, 3.9]
Medication (1=Olanzapine, 2=Risperidone)	1.3	[0.3, 4.6]	1.1	[0.7, 1.7]
Site (0 = Hillside, 1 = Bronx)	1.7	[0.4, 8.0]	5.4 ^{***}	[3.3, 8.9]
Sex (1 = male, 2 = female)	3.4	[0.8, 14.4]	0.6	[0.3, 1.2]
Age	1.0	[0.9, 1.2]	1.0	[1.0, 1.1]
Socioeconomic Status	0.9	[0.9, 1.0]	1.0	[1.0, 1.0]
Black	1.2	[0.1, 12.2]	1.2	[0.5, 2.8]
Latino	7.9	[0.6, 104.2]	0.5	[0.2, 1.6]
Race: (ref = white)				
Asian	4.7	[0.4, 57.9]	[†]	
Other	2.0	[0.1, 37.6]	2.4 ⁺	[0.9, 6.1]
Model Fit χ^2	18.9 [*]		92.1 ^{***}	
# Participants	103		96	
# "Failure" Events	12		90	
Months at risk	986		927	
Results illustrated in	Figure 1		Figure 2	

Note: Cannabis Use is a time-varying covariate; all other predictors are time-invariant.

⁺ p < .10

^{*} p < .05

^{**} p < .01

^{***} p < .001.

[†] Asians had to be excluded from this analysis because there were no months during which an Asian participant both had valid data for cannabis use and was observed to be non-adherent.