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Marijuana use in the immediate 5-year premorbid period is associated with increased risk of onset of schizophrenia and related psychotic disorders

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ABSTRACT

Objectives: Several studies suggest that adolescent marijuana use predicts earlier age at onset of schizophrenia, which is a crucial prognostic indicator. Yet, many investigations have not adequately established a clear temporal relationship between the use and onset.
Methods: We enrolled 247 first-episode psychosis patients from six psychiatric units and collected data on lifetime marijuana/alcohol/tobacco use, and ages at onset of prodrome and psychosis in 210 of these patients. Cox regression (survival analysis) was employed to quantify hazard ratios (HRs) for effects of diverse premorbid use variables on psychosis onset.
Results: Escalation of premorbid use in the 5 years prior to onset was highly predictive of an increased risk for onset (e.g., increasing from no use to daily use, HR = 3.6, $p < 0.0005$). Through the analysis of time-specific measures, we determined that daily use approximately doubled the rate of onset (HR = 2.2, $p < 0.0005$), even after controlling for simultaneous alcohol/tobacco use. Building on previous studies, we were able to determine that cumulative marijuana exposure was associated with an increased rate of onset of psychosis ($p = 0.007$), independent of gender and family history, and this is possibly the reason for age at initiation of marijuana use also being associated with rate of onset in this cohort.
Conclusions: These data provide evidence of a clear temporal relationship between escalations in use in the five years pre-onset and an increased rate of onset, demonstrate that the strength of the association is similar pre- and post-onset of prodromal symptoms, and determine that early adult use may be just as important as adolescent use in these associations.

1. Introduction

Recent evidence shows a link between marijuana use and psychotic disorders, and this association has remained significant when controlling for other substance use (van Os et al., 2002; Zammit et al., 2002; Barnes et al., 2006; Gonzalez-Pinto et al., 2008). Subsequent reports have thus tried to determine the origins of this link; specifically, whether there is merely shared etiology or a possible causal relationship. One key piece of evidence for causation would be a temporal relationship between the initiation of substance use and the onset the disorder. A number of studies have shown that marijuana use often predates onset of psychotic disorders, providing some evidence of a possible causal link (Allebeck et al., 1993; Arseneault et al., 2002; Buhler et al., 2002; Zammit et al., 2002; Semple et al., 2005; Mauri et al., 2006). However, these analyses have only been able to demonstrate broadly defined temporal links, and most studies have not specifically targeted premorbid use as a predictor.

To further refine evidence of the causal hypothesis, later empirical efforts focused specifically on the link between marijuana use and age at onset of psychosis (Van Mastrigt et al., 2004; Veen et al., 2004;

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Barnes et al., 2006; Gonzalez-Pinto et al., 2008; Compton et al., 2009b; Sevy et al., 2010; Large et al., 2011), rather than a diagnosis of a psychotic disorder. However, these studies present methodological challenges, such as varying definitions of onset. While some have used age at initiation of treatment (Fergusson et al., 2005; Di Forti et al., 2014), others have used personal histories to determine the age at first psychotic symptom. Given that there are typically highly variable durations of treatment delays, using age at first treatment may not offer the best evidence of a causal link.

A possible causal association would also be supported if there were a dose–response relationship. However, most studies of substance use (Hambrecht and Hafner, 1996; Rabinowitz et al., 1998; Van Mastrigt et al., 2004), and marijuana use in particular (Buhler et al., 2002; Green et al., 2004; Barnes et al., 2006), were comparisons of those meeting abuse/dependence criteria (current or lifetime) with a suitable control group, or comparisons of users at any level to nonusers (Arseneault et al., 2002; Zammit et al., 2002; Veen et al., 2004; Moore et al., 2007; Di Forti et al., 2014). Only a few investigations have been able to assess frequency/amount of use or change in use over time, and these were limited to broad use level categories. Even so, there has been evidence that more frequent use is associated with an increased risk of psychosis (van Os et al., 2002; Zammit et al., 2002; Fergusson et al., 2005), as well as earlier onset of psychosis (Gonzalez-Pinto et al., 2008). In addition, it has been shown that faster *progression* to high levels of use is also associated with increased risk of psychosis (Boydell et al., 2006) and earlier onset (Compton et al., 2009b). Age of initiation of marijuana use is also associated with age at onset of psychosis (Arseneault et al., 2002; Leeson et al., 2012; Stefanis et al., 2013; Di Forti et al., 2014) indicating a possible cumulative dose effect. The resulting interpretations of these data could be confirmed through the use of more detailed retrospective information.

Additionally, there is often a prodromal period during which evidence of an emerging disorder is present, though not yet clinically manifest. Marijuana use during that period would also be of interest when trying to determine any possible links to development of the full disorder. A few studies have shown that marijuana use was also a predictor of onset of psychiatric symptoms (the prodrome), as well as onset of psychosis (Compton et al., 2009b; Leeson et al., 2012). However, onset of the prodrome is coincident with onset of psychosis for some patients, either due to actual illness course or possible measurement error. Thus, a more comprehensive assessment of the effects on onset of prodromal symptoms would be to evaluate its role as a possible moderator of the relationship between use and risk of onset.

The current study was designed specifically to address these issues by providing a thorough retrospective assessment of *premorbid* marijuana use, from age 12 until psychosis onset, in a well-defined and extensively characterized sample of first-episode patients. This allowed us to focus on quantitative amounts of use in the time immediately preceding psychosis onset in order to establish a more clearly defined temporal link, while simultaneously examining dose-related effects. These data also gave the unique opportunity to test for the effects of use at specific time periods in order to clarify key outstanding questions in the literature. While this is the most comprehensive dataset to date to test these effects, we acknowledge that any retrospective assessment is subject to recall error or bias, and thus the demonstrated relationships should be interpreted with that caveat in mind.

2. Method

2.1. Settings and subjects

Consecutively admitted patients with first-episode psychosis were approached for study participation. N = 247 were enrolled from August 2008 to June 2013 from three inpatient psychiatric units in Atlanta, Georgia and three in Washington, D.C. Eligible patients were 18–40 years of age, English-speaking, and able to give informed consent. Exclusion criteria included known or suspected mental retardation, a Mini-Mental State Examination (Folstein et al., 1975; Cockrell and Folstein, 1988) score of <24, or presence of a major medical condition compromising ability to participate. Once psychotic symptoms were stabilized sufficiently for informed consent and participation, trained masters- or doctoral-level assessors conducted the in-depth assessments. When possible, collateral assessments were also conducted with family members/informants. This information was used along with participant data when arriving at consensus-based best estimates for several key measures. Research diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1998). An adapted version of the Family Interview for Genetic Studies (FIGS; Maxwell, 1992) was used to collect detailed data on family history of psychotic symptoms and disorders; participants were then classified according to first-degree family history of narrowly defined schizophrenia or a broadly defined psychotic disorder. All study procedures were approved by all relevant Institutional Review Boards.

SCID-based diagnoses included the following: schizophrenia, paranoid type (97, 39%); psychotic disorder, not otherwise specified (38, 15%); schizophrenia, undifferentiated type (33, 13%); schizophreniform disorder (29, 12%); schizoaffective disorder, depressive type (26, 11%); schizophrenia, disorganized type (11, 5%); schizoaffective disorder, bipolar type (5, 2%); delusional disorder (4, 2%); brief psychotic disorder (2, 1%); and schizophrenia, catatonic type (2, 1%).

Sociodemographic characteristics of the sample—and the subsample used in these analyses—are given in Table 1. Of the 247 participants enrolled, 15 could not have their age at onset of psychosis determined and thus were removed from the presented analyses. Of the remaining subjects, 22 could not have their complete lifetime substance use assessed, leaving a sample size of 210 for the current analyses. The subjects removed were not significantly different from those in the presented data on any measures.

2.2. Measures

2.2.1. In-depth assessment of premorbid substance use

All substance use was assessed using the Lifetime Substance Use Recall (LSUR) instrument—designed specifically for this study and described previously in terms of development and validity (Ramsay et al., 2011)—which recorded average use per calendar year, beginning with age 12 and continuing to the index hospitalization. Marijuana use was recorded in joints per month, alcohol use in drinks per month, and tobacco use in cigarettes per month; these data were then multiplied by 12 to get a reported total number of joints, drinks, and cigarettes per year for each subject (see Appendix A for calculations). The span of use variables in the sample ranged from a single year up to 25 years. The month and year of onset of psychosis were used as a threshold to determine that all use variables included in the analysis were in fact measuring *premorbid* use (i.e., before the onset of any reported

Table 1
Sociodemographic characteristics of study subjects.

Characteristic	All subjects recruited into the study (N = 247)		Subsample of subjects included in the analysis (N = 210)	
	Mean	SD	Mean	SD
Age (years)	23.9	4.8	23.9	4.9
Years of education	11.9	2.2	11.9	2.2
	N	%	N	%
Male gender	184	74.5	159	75.7
African American race	213	86.2	181	86.2
Single and never married	213	86.2	182	86.7
Living with parents/relatives	162	65.6	138	65.7
Unemployed in the month prior to hospitalization	169	68.4	146	69.5

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