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Pre-Illness Cannabis Use and the Early Course of Nonaffective Psychotic Disorders: Associations with Premorbid Functioning, the Prodrome, and Mode of Onset of Psychosis

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Abstract

Introduction—Limited research indicates that pre-illness cannabis use may result in an earlier age at onset of psychosis, though little is known about the influence of prior cannabis use on the premorbid and prodromal phases. This study examined effects of prior or concurrent cannabis (as well as nicotine and alcohol) use on: (1) early adolescent (12–15 years) premorbid functioning, (2) late adolescent (16–18 years) premorbid functioning, (3) two features of the prodrome, and (4) mode of onset of psychosis.

Methods—Participants included 109 well-characterized first-episode patients hospitalized in public-sector settings. Assessments included ages at initiation of first, weekly, and daily use of substances, the *Premorbid Adjustment Scale*, the *Symptom Onset in Schizophrenia* inventory, and a consensus-based best estimate of mode of onset.

Results—Participants having used cannabis at ≤15 years had better early adolescence social functioning than those who had not used cannabis (p=0.02). Conversely, those who had used cannabis at ≤18 years had poorer late adolescence academic functioning (p<0.001). Participants having used cannabis before onset of psychotic symptoms did not differ from those who had not in terms of having had an identifiable prodrome or the number of prodromal symptoms experienced. Whereas 42% of those having used cannabis daily had an acute mode of onset of psychosis, only 20% of those without prior daily cannabis use had an acute onset (p=0.04).

Conclusions—Findings suggest that cannabis use is associated with premorbid social and academic functioning and mode of onset. Further research is warranted to elucidate the complex associations between cannabis use and diverse early-course features.

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Conflicts of Interest
The authors know of no conflicts of interest pertaining to this research or this article.

Contributors
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Keywords

Cannabis; First-episode psychosis; Marijuana; Mode of onset; Premorbid functioning; Prodrome; Psychosis; Schizophrenia

1. Introduction

Among individuals with schizophrenia, the most commonly abused substances are nicotine, alcohol, cannabis, and cocaine (Mueser & McGurk, 2004). Cannabis misuse is of particular interest for several reasons. First, cannabis appears to be the most commonly abused substance in samples of patients with schizophrenia (DeQuardo et al., 1994; Sevy et al., 2001), including first-episode patients (Barnett et al., 2007; Van Mastrigt et al., 2004). Second, pre-illness cannabis use may be an independent risk factor for psychosis (Semple et al., 2005) and appears to be associated with an earlier onset of psychotic symptoms (Barnes et al., 2006; Compton and Ramsay, 2009). Third, even among first-episode patients, heavy substance use, including cannabis use, is associated with increased risk of inpatient admission, poorer symptomatic and functional outcomes, and shorter time to relapse (Wade et al., 2006, Wade et al., 2007). Further research is needed to examine how cannabis use influences early-course features, given that premorbid functioning, prodromal features, age at onset, and mode of onset of psychosis each has prognostic implications for the longer-term course of nonaffective psychotic disorders.

A previous report from the present first-episode sample documented associations between pre-illness cannabis, alcohol, and tobacco use and the age at onset of prodrome and age at onset of psychosis; specifically, analysis of change in frequency of use prior to onset indicated that progression to daily cannabis and tobacco use was associated with an increased risk of onset of psychotic symptoms, and similar or even stronger effects were observed when onset of illness or prodromal symptoms was the outcome (Compton et al., 2009a). (However, it should be noted that it has been suggested that the association between age at onset and cannabis use is a spurious one because those using cannabis are more likely to be young; Wade, 2005). Yet, aside from associations with age at onset, very little is known about the influence of cannabis use on these other aforementioned early-course features. Given the sequential onset of nonaffective psychotic disorders and the need to further characterize early-course epochs including the premorbid and prodromal phases, this study examined the effects of prior or concurrent cannabis (as well as nicotine and alcohol) use on: (1) premorbid functioning in early adolescence (12–15 years), (2) premorbid functioning in late adolescence (16–18 years), (3) two features of the prodrome (presence of a retrospectively identifiable prodrome and the number of prodromal features experienced), and (4) mode of onset of psychosis.

2. Methods

2.1. Setting and Sample

This analysis was conducted using data from a well-characterized sample of first-episode patients enrolled in a study on the determinants of treatment delay, or the duration of untreated psychosis (Compton et al., 2008; Compton et al., 2009b; Compton et al., 2009c; Compton et al., 2010a). The sample included individuals, aged 18–40 years, who were hospitalized for recent-onset or previously untreated nonaffective psychosis at a large, urban, university-affiliated, public-sector hospital (n=99) or an suburban county psychiatric crisis center (n=10). Exclusion criteria included: known or suspected mental retardation, a Mini-Mental State Examination (Cockrell et al., 1988; Folstein et al., 2001) score of <23, a significant medical condition compromising ability to participate, prior antipsychotic

treatment of >3 months duration, previous hospitalization for psychosis >3 months prior to the index hospitalization, or inability to provide written informed consent.

Demographic and clinical characteristics of the present sample have been described in detail elsewhere (Compton et al., 2010a; Compton et al., 2010b). Briefly, participants' mean age at recruitment was 23.1±4.7 years. The majority of the sample was male (76.1%) and African American (89.9%). Coming from a socioeconomically disadvantaged milieu, many participants had not completed high school (44.0%, Goulding et al., 2010), reported a prior history of incarceration (57.8%, Ramsay et al., 2010), and were unemployed (61.5%) at the time of treatment contact. All participants met *Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID; First et al., 1998) criteria for schizophreniform disorder, schizophrenia, schizoaffective disorder, brief psychotic disorder, delusional disorder, or psychotic disorder not otherwise specified, as described in greater detail elsewhere (Compton et al., 2010a; Compton et al., 2010b).

2.2. Procedures and Materials

Participants were first approached several days after their admission to the inpatient units, allowing for adequate stabilization of symptoms and initiation of treatment planning. The research assessment typically lasted 3–4 hours and occurred on hospital day 9.1±6.7. Data on substance use were collected by inquiring about the age at initiation of any use, weekly use, and daily use of cannabis, alcohol, and tobacco (Compton et al., 2009a; Stewart et al., 2010). As noted previously (Stewart et al., 2010), the majority of participants (87, 79.8%) had previously used cannabis; furthermore, 66 (60.6%) had used it weekly and 49 (45.0%) had previously used it daily.

The *Premorbid Adjustment Scale* (PAS; Cannon-Spoor et al., 1982), a reliable and valid instrument widely used in schizophrenia research, was used to assess the degree of attainment of specific developmental goals preceding initial onset of psychosis (Alvarez et al., 1987; Cannon-Spoor et al., 1982). Premorbid functioning was rated (0–6 for normal to severe impairment) during two age periods: early adolescence (12–15 years) and late adolescence (16–18 years), in two domains typically considered as subscales of the PAS. That is, in both early adolescence and late adolescence, *academic functioning* is comprised of scholastic performance and adaptation to school, and *social functioning* includes sociability and withdrawal, peer relationships, and social-sexual functioning. As described in a previous report (Monte et al., 2008), premorbid functioning was not assessed in the early or late adolescence age periods if these periods included the year before the onset of prodromal symptoms, as a conservative measure to safeguard against inadvertently assessing prodromal impairments during the rating of premorbid functioning.

As described previously (Compton et al., 2010b), a consensus-based determination of the presence of a prodrome relied on both patient and informant/family member data derived from the *Symptom Onset in Schizophrenia* (SOS) inventory (Perkins et al., 2000) and select items from the semi-structured *Course of Onset and Relapse Schedule/Topography of Psychotic Episode* (CORS/TOPE) interview (Norman et al., 2002). Regarding the latter, participants were asked questions such as: "When were you last your usual self?", "When did you first notice a change?", "What was the first change that you noticed?", "What do you believe is the cause of these problems that you are currently having?", and "When did you think that it was important to seek help for yourself?" The SOS elicits information about 14 well-defined symptoms that are commonly observed during the prodromal phase of psychotic disorders. Each item is rated on a 4-point scale based on the frequency and duration of the disturbance, which determines whether it was clinically relevant as a harbinger of the subsequent psychotic episode. Of note, non-specific features such as dysphoric mood must be relatively more severe, while attenuated or brief psychotic

experiences may be considered a marker of the subsequent disorder after occurring only a few times. To qualify as prodromal, each symptom had to have a recognizable onset (as opposed to being characterological in nature) and had to be contiguous (without clearly discernible periods of wellness intervening) with the subsequent onset of psychosis (Keshavan et al., 2003). A prodrome was considered present if one or more of the 14 items was rated at a clinically significant level before onset of frank psychotic symptoms; severity was operationalized as the number of such symptoms present.

As outlined by the World Health Organization's International Pilot Study of Schizophrenia (Jablensky et al., 1992), and described elsewhere (Compton et al., 2008) mode of onset of psychotic symptoms was operationalized as acute with sudden onset, acute with precipitous onset, subacute, gradual, and insidious. These five levels were trichotomized as *acute* (comprised of the sudden and precipitous categories), *subacute*, and *chronic* (including gradual and insidious categories). Mode of onset was determined using a consensus-based best estimate approach using all available information from patients, clinicians, and informants/family members.

2.3. Data Analyses

The effects of cannabis use on early and late adolescent premorbid social and academic functioning were examined using independent samples Student's *t*-tests, followed by factorial analyses of variance (ANOVAs) to account for the effects of gender as needed. Associations between cannabis use prior to the onset of psychosis and two features of the prodrome relied on a chi-square test and a Mann-Whitney *U*-test. The relation between cannabis use and mode of onset of psychosis was assessed with a chi-square test. Analyses were conducted using the *SPSS 16.0* statistical package, and all tests relied on a two-tailed $p \leq 0.05$ as the criterion for significance.

3. Results

3.1. Influence of Prior or Concurrent Substance Use on Early Adolescent Premorbid Functioning

Participants who had used cannabis before or at the age of 15 years (n=49) were compared to those who had not used cannabis before or at the age of 15 years (n=60) on PAS early adolescence (12–15 years of age) social and academic scores. As shown in Table 1, those who had used cannabis had a mean PAS early adolescence social score of 1.21±0.85, compared to 1.75±1.27 in those who had not used (t=2.34, df=95, p=0.02), indicating *better* social functioning among those having used cannabis. In contrast to premorbid social functioning, PAS early adolescence academic scores did not differ between the two groups, though the mean score for those with a history of cannabis use was numerically higher (suggesting poorer academic functioning) than that for those who had not used cannabis.

Similar comparisons were conducted with regard to having used nicotine before or at the age of 15 (n=43, compared to n=66 who had not) and having used alcohol before or at the age of 15 (n=45, compared to n=64 who had not). Regarding nicotine, the two groups did not differ on either of the PAS early adolescence scores. However, like the finding pertaining to prior cannabis use, those who had used alcohol had a lower mean PAS early adolescence social score (1.24±0.98) compared to those who had not (1.69±1.20; t=1.97, df=95, p=0.05). Gender was not significantly associated with PAS early adolescence scores in either social or academic domains.

3.2. Influence of Prior or Concurrent Substance Use on Late Adolescent Premorbid Functioning

Participants who had used cannabis before or at the age of 18 years (n=77) were compared to those who had not used cannabis before or at the age of 18 years (n=32) on PAS late adolescence (16–18 years of age) social and academic scores (also shown in Table 1). Of note, only 73 participants were rated for late adolescence premorbid functioning because those who entered the prodromal period prior to the age of 19 were not rated, as noted above. Furthermore, the group having used cannabis before or at the age of 18 years included those having used cannabis before or at the age of 15 years, who were considered previously. The mean PAS late adolescence social score did not differ significantly between the two groups. However, those who had used cannabis had a mean PAS late adolescence academic score of 3.59±1.46, compared to 2.00±1.33 (t=−4.52, df=65, p<0.001).

Again, similar comparisons were conducted with regard to having used nicotine before or at the age of 18 (n=69, compared to n=40 who had not) and having used alcohol before or at the age of 18 (n=82, compared to n=27 who had not). Those who had used nicotine had a mean PAS late adolescence academic score of 3.59±1.46, compared to 2.00±1.33 (t=−4.52, df=65, p<0.001). The two groups did not differ on PAS late adolescence social scores. Similarly, those with a history of alcohol use had a mean PAS late adolescence academic score of 3.33±1.54, compared to 1.82±1.24 (t=−3.64, df=65, p=0.001), though again, the two groups did not differ on PAS late adolescence social scores.

Gender was not statistically significantly associated with PAS late adolescence social scores, but female participants had a lower mean late adolescence academic score (2.25±1.35) than male participants (3.22±1.62; t=−2.31, df=65, p=0.02). Factorial (2 x 2) ANOVAs revealed no significant interaction effects, though cannabis use (F=12.92, p=0.001), nicotine use (F=13.73, p<0.001), and alcohol use (F=11.46, p=0.001) before or at the age of 18 years remained a significant predictor of PAS late adolescence academic scores in each respective model even when considering the effects of gender.

3.3. Cannabis Use Prior to the Onset of Psychosis as a Predictor of Prodromal Features

Participants who reported having used cannabis before the onset of psychotic symptoms (n=73) were compared to those who had not used cannabis before the onset of psychotic symptoms (n=26) in terms of having experienced a retrospectively identified prodrome. Fifty-one patients (69.9%) who had used cannabis prior to the onset of psychotic symptoms had a prodrome, compared to 21 (80.8%) of those who had not used cannabis (χ^2=1.15, df=1, p=0.32). A similar comparison of percentages in terms of having used daily before the onset of psychosis (n=39, 39.4%) versus not having used daily (n=60, 60.6%), again revealed no statistically significant association with presence or absence of a prodrome. A previous analysis revealed that those who had and had not experienced a prodrome did not differ with respect to gender (Compton et al., 2010).

Prior cannabis use also was not predictive of the number of prodromal features experienced. Those who had used cannabis daily prior to onset of psychosis had a mean number of 5.9±3.1 symptoms, compared to 5.5±2.5 among those who had not used cannabis daily (Mann-Whitney U-test z=0.28, p=0.79). Gender was not associated with the number of prodromal features.

3.4. Substance Use Prior to the Onset of Psychosis as a Correlate of Mode of Onset of Psychosis

Participants who reported having used cannabis daily before the onset of psychotic symptoms (n=38) were compared to those who had not (n=60) in terms of mode of onset of

psychosis. Whereas 16 (42.1%) of those having used daily had an acute mode, only 12 (20.0%) of those without past daily cannabis use had an acute mode (χ^2=6.53, *df*=2, *p*=0.04). Conversely, 9 (23.7%) of those who had used daily had a subacute mode, compared to 26 (43.3%) of those who had not used daily. A chronic mode of onset was recorded for 13 (34.2%) of those with a history of daily use and 22 (36.7%) of those without daily use. Mode of onset was not significantly associated with gender, daily nicotine use prior to the onset of psychosis, or weekly alcohol use prior to onset.

4. Discussion

Four key findings emerged from these analyses. First, participants who reported having used cannabis before or at the age of 15 years had better social functioning in early adolescence (but not late adolescence) than those who had not. Second, those who had used cannabis before or at the age of 18 years had poorer academic functioning than those who had not. Third, cannabis use was not associated with the presence of a retrospectively identified prodrome or the number of prodromal symptoms experienced. Fourth, prior cannabis use was associated with a greater likelihood of an acute mode of onset and a lesser likelihood of a subacute mode.

Several previous examinations of the relationship between substance use and premorbid functioning have found that those endorsing substance use have better premorbid social functioning (Carr et al., 2009; Larsen et al., 2006) and poorer premorbid academic functioning (Carr et al., 2009; Larsen et al., 2006; Petersen et al., 2007; Ringen et al., 2008); though most of these studies evaluated substance use in general. The most likely explanations for the past and current findings are: (1) individuals with better social functioning may be more prone to cannabis use because of increased social contacts (Larsen et al., 2006; Salyers and Mueser, 2001), (2) a certain level of social sophistication is required to procure cannabis at such an early age due to the illegal status of the substance (Larsen et al., 2006; Salyers and Mueser, 2001), and (3) consistent with research in non-psychotic populations (Jacobus et al., 2009; Schweinsburg et al., 2008), cannabis use is detrimental to school functioning in adolescence.

Though cannabis use has been identified as a potential risk factor for earlier onset of psychosis (Barnes et al., 2006; Barnett et al., 2007; Compton et al., 2009a; Van Mastrigt et al., 2004), results examining the association of cannabis use and later conversion to psychosis in high-risk samples have been mixed (Kristensen and Cadenhead, 2007; Phillips et al., 2002). Retrospective investigations of age at onset of the prodrome in first-episode samples have revealed an earlier age at onset for patients who used substances compared to those who had not (Compton et al., 2009a; Hambrecht and Häfner, 2000). When examining the effects of cannabis use on the prodrome in high-risk samples, associations have been found with incidence (Miettunen et al., 2008) and severity of prodromal symptoms (Corcoran et al., 2008), though the present retrospective study failed to find an association between cannabis use and presence of a prodrome or number of prodromal symptoms. Further examination of the influence of substance use (especially cannabis use) on prodromal features is needed (Compton and Ramsay, 2009).

Few studies have tested for associations between substance use and the mode of onset of psychosis in nonaffective psychotic disorders. While two older studies suggested that substance misuse has no discernible impact on the acuity of psychosis (Cantwell et al., 1999; McGuire et al., 1994), Mazzoncini and colleagues (2010) found that first-episode patients with comorbid cannabis misuse were significantly more likely to have had an acute mode of onset. Differential characteristics of the onset of primary and substance-induced psychoses may be informative in determining a diagnosis. Caton and colleagues (2007) underscore the

challenges of this distinction in a longitudinal study of patients newly diagnosed with substance-induced or primary nonaffective psychotic disorders; approximately one-tenth of patients in each group were diagnostically reclassified after one year.

Several methodological limitations should be considered. First, the cross-sectional design required retrospective self-report of all substance use-related data, and recall biases cannot be excluded (e.g., memory can be impaired by recent cannabis use; Miller et al., 1977). Second, analyses would ideally examine the independent effects of cannabis, nicotine, and alcohol use, though this could not be done in the present analysis (for example, pertaining to late adolescence academic functioning) due to the level of comorbidity across substances. Additionally, the potential confounding effects of the use of other drugs, such as cocaine, could not be controlled; however, only a very small proportion of participants had used such drugs, and when they had, such use was typically very sporadic. Cannabis is by far the most commonly and consistently used illicit substance in this sample. Third, the present study utilized a sample primarily composed of African American males, and generalizability to dissimilar populations may be limited. Fourth, although it would be of interest to assess the effects of differences in age at onset of cannabis use and premorbid functioning, because the group having used cannabis before or at the age of 18 years included those having used cannabis before or at the age of 15 years, possible age-related effects could not be completely examined (partly because there was a relatively small group of participants initiating cannabis use between the ages of 16 and 18 years). The *a priori* hypotheses focused on the effects of any pre-illness cannabis use on premorbid functioning rather than possible effects of age at onset of use. Despite the inherent limitations, the findings generally replicate several prior reports and indicate an influence of cannabis on several key early-course features in addition to its recently reported impact on the age at onset of psychotic symptoms.

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Table 1

Associations between Prior or Concurrent Cannabis Use and Social and Academic Premorbid Functioning

PAS Domain	Prior or Concurrent Use of Cannabis	No Prior or Concurrent Use of Cannabis	Test Statistic, df, p
Early Adolescence – Social	1.21±0.85	1.75±1.27	t=2.46, df=95, p=0.02
Early Adolescence – Academic	2.06±0.79	1.81±0.96	t=−1.40, df=102, p=0.17
Late Adolescence – Social	1.42±1.06	1.67±0.95	t=1.04, df=71, p=0.30
Late Adolescence – Academic	3.59±1.46	2.00±1.33	t=−4.52, df=65, p<0.001