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The Relationship between Alcohol/Cannabis Use and
Symptom Profile and Progression in Individuals at Risk for Psychosis

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By

Molly K. Larson
M.A., Emory University, 2006

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An abstract of
A dissertation submitted to the Faculty of the
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Abstract

The Relationship between Alcohol/Cannabis Use and
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By Molly K. Larson

Alcohol and cannabis are the most commonly used substances among persons with schizophrenia and other psychotic disorders and often associated with a poorer prognosis. Recent research indicates that better social functioning and fewer negative symptoms are associated with alcohol use early in the course of the illness, however, worse negative and positive symptoms are often found later. A mounting body of evidence suggests that cannabis use appears to confer increased risk of psychosis. Furthermore, research suggests that poorer outcome, including more hospitalizations and lower functioning scores, as well as worse positive symptoms and greater overall severity of illness is associated with cannabis dependence and abuse. There is a dearth of prospective studies examining the relation between alcohol and cannabis use in individuals designated as prodromal based on the presence of subclinical psychotic symptoms. Furthermore, there are no published reports on the independent and/or interactive effect of these substances.

The current study extends the literature by examining the association of symptom profile and progression with varying levels of alcohol and cannabis use in a putatively prodromal sample. Participants (N=888) were recruited at eight study sites as part of the North American Prodrome Longitudinal Study. Participants with symptom and substance use data at baseline (N=710) were examined for an association between current symptom severity and substance use. Participants with both baseline and six-month follow-up data (N=297) were examined for the relation between substance use at baseline and symptom severity at follow-up. An interactive effect of these substances on symptom severity at baseline was found. Less severe negative symptoms are associated with moderate alcohol use and abstinence from cannabis. In contrast, those who report no alcohol use, or alcohol abuse/dependence and cannabis use, showed more severe negative symptoms. More severe positive symptoms are associated with increased levels of cannabis and alcohol use. No significant results were found for the association between substance use and symptom progression. These findings point to the importance of jointly examining the effects of substances that have a high rate of co-occurrence, in that interactive and independent effects are elucidated. The results are discussed in the context of potential mechanisms.

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Introduction

Schizophrenia is a debilitating disease that affects 1% of the population (American Psychiatric Association, DSM-IV-TR, 2000). The clinical presentation of schizophrenia is characterized by positive and negative symptoms. Positive symptoms reflect an excess or aberration of normal perception, emotion, or thought, and may be characterized as psychotic or disorganized. Hallucinations and delusions are considered psychotic symptoms, while disordered speech, thinking, or behaviors represent the disorganized dimension. In contrast, negative symptoms are associated with diminution or absence of normal emotion, thought, speech, or goal-oriented behavior. General symptoms, such as anxiety, depression, and sleep disturbances, often accompany the clinical presentation of schizophrenia. The onset of the clinical syndrome is usually preceded by a prodromal period of sub-clinical signs and symptoms. This can last from months to several years, and comorbid disorders are very common during this prodromal period (Rosen, Miller, D'Andrea, McGlashan & Woods, 2006).

Research indicates that substance use (SU) is prevalent in persons diagnosed with schizophrenia and other psychoses (other schizophrenia spectrum disorders including schizophreniform disorder and schizoaffective disorder, as well as other psychotic disorders such as delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to medical condition, substance-induced psychotic disorder, and psychotic disorder not otherwise specified) and is associated with a poorer prognosis, including longer duration of illness episodes, more frequent hospitalizations and poorer functional recovery

(Stefanis, Delespaul, Henquet, Bakoula, Stefanis, & Van Os, 2004). Recent research is also beginning to suggest that SU is common in the prodromal period, with as many as 25-50% of substance-using patients reporting use one to three years prior to the clinical onset of schizophrenia (Bersani, Orlandi, Kotzalidis, & Pancheri, 2002; Boydell, Dean, Dutta, Giouroukou, Fearon, & Murray, 2007; Hambracht & Hafner, 2000).

The substances most commonly used by patients with psychotic disorders are alcohol and cannabis (Childers & Harding, 1990; Kamali, Kelly, Gelvin, Browne, Ldarkin & O'Callaghan, 2000; Rosen, Miller, D'Andrea, McGlashan & Woods, 2006). Although research has demonstrated that the use of these substances is linked with poorer prognosis, the extant literature on the relation of the substances with symptoms has not addressed the prodromal period. This study is aimed at examining the relation of both alcohol and cannabis with the prodromal signs of psychosis.

Schizophrenia and other psychotic disorders are among the most debilitating mental disorders because multiple facets of functioning are negatively affected by the disorder and while treatments are improving every year, the life of someone with a psychotic disorder is often marked by multiple hospitalizations and a lifetime of antipsychotic medication use. As we are far from a "cure" for schizophrenia, prevention is vital. Identification of those most at risk for developing a psychotic disorder is the first step to prevention. The onset of psychosis may be preceded by months or years of psychological and behavioral abnormalities including disturbances in cognition, emotion, perception,

communication, motivation and sleep (Arseneault, Cannon, Witton, & Murray, 2004).

The fact that deficits in these areas of functioning negatively impacts social, emotional, and cognitive development makes early detection and intervention especially important. Recent research suggests that persons at risk for developing a psychotic disorder or who are already psychotic evidence unique vulnerability to the effect of substances on brain systems. Specifically, this vulnerability appears to infer increased sensitivity such that smaller doses of substances bring about detrimental effects (Drake & Wallach, 1989; D'Souza, Abi-Saab, Madonick, Forselius-Bielen, Doersch, Braley, et al., 2005). Furthermore, SU interferes with education, social and emotional development, and brain maturation (Kavanagh, 2008). Thus, SU may further impair healthy development of areas affected by psychosis and the prodrome to schizophrenia and other psychotic disorders. This makes adolescents who are both at risk for developing psychosis and using substances uniquely vulnerable to developing schizophrenia and other psychotic disorders. In addition, evidence that untreated psychosis has deleterious effects on the brain and the course of the illness (Lieberman, Perkins, Belger, Chakos, Jarskog, Boteva, et al., 2001) supports the notion that early intervention may positively impact outcome.

There is contention in the literature regarding the causal relationship implicated by findings that alcohol use (AU) and cannabis use (CU) are related to the course of illness and the symptom profile of persons with, and at risk for, schizophrenia and other psychotic disorders. Necessary evidence to conclude that

SU is a contributing cause for developing a psychotic disorder would include, but not be limited to: a) a relation of SU with the course or profile of symptoms; b) a dose-dependent relationship; c) temporality, that is, evidence of use prior to onset of the disease or symptom exacerbation; and d) empirical or theoretical evidence for potential mechanisms of action (Arseneault, Cannon, Witton & Murray, 2004; Thornicroft, 1990). Evidence for sole causality is unlikely. Research suggests that induction of schizophrenia spectrum disorders and other psychotic disorders solely by AU or CU is uncommon and often transient (for example, alcohol hallucinosis in the instance of acute alcohol intoxication, or reports of psychotic-like symptoms that do not persist beyond the period of cannabis intoxication). However, in some cases psychosis following SU may be a reflection of precipitation of underlying vulnerabilities that have been triggered or exacerbated.

The present study first presents a review of the extant literature on the effects of alcohol and cannabis on psychosis and then aims to extend the current knowledge by examining the association between symptom profile and progression and alcohol and cannabis use in individuals designated as prodromal based on the presence of subclinical psychotic symptoms. Putatively prodromal patients were assessed for both symptom presentation and substance use at baseline and again six months later at eight sites in North America.

To provide a background for the current study, a brief introduction to the prodrome to schizophrenia and other psychotic disorders will be followed by a review of the literature on the association between nonspecific SU and psychosis. This is followed by a review of the specific relations of AU and CU with

psychosis. This literature review will also address current hypotheses about the potential moderators and mechanisms underlying the relationship between SU and schizophrenia and other psychotic disorders. In particular, evidence bearing on the causal relationship between SU and psychosis will be discussed. Next, the current study of SU in prodromal patients will be described. Results will be presented on analyses of the baseline (cross-sectional) and follow-up data (longitudinal). Finally, implications, conclusions, and limitations of the current research will be discussed.

The Prodrome to Schizophrenia and Other Psychotic Disorders

The prodrome to schizophrenia and other psychotic disorders is characterized as a process of changes or deterioration in heterogeneous subjective and behavior symptoms that precede the onset of clinical psychotic symptoms. Prodromal individuals are often help-seeking adolescents experiencing mild or moderate disturbances in perception, cognitive, language, motor function, will, initiative, level of energy, and stress tolerance (Olsen & Rosenbaum, 2006). This period of prepsychotic disturbance in which attenuated or subthreshold psychotic features begin to manifest differs from frank psychotic features in intensity, frequency and/or duration. The threshold, albeit relatively subjective and arbitrary, is based on symptom severity and treatment implications such that the presence of psychotic symptoms that would warrant antipsychotic medication treatment signifies the end-point of the prodromal period (Yung, Yuen, McGorry, Phillips, Kelly, Dell'Olio, et al., 2005).

In an attempt to better categorize the prodromal period to schizophrenia and other psychotic disorders, and to elucidate the process of change or deterioration that represents a deviation from an individual's previous experience or behavior (Yung & McGorry, 1996), researchers have proposed the following phases of increasingly high-risk mental states. In general, individuals first experience negative or nonspecific clinical symptoms such as depression, anxiety symptoms, social isolation and school/occupational failure. This is often followed by the emergence of brief intermittent attenuated positive symptoms of moderate intensity. Most proximal to psychosis, individuals exhibit severe attenuated positive symptoms that remain subpsychotic in terms of frequency (once or twice a month), duration (often lasting for only a few minutes and usually less than a day), and intensity (skepticism as to the veracity of hallucinations or delusions can still be induced; an der Heiden, & Hafner, 2000; Cornblatt, Lencz, Smith, Correll, Auther, Nakayama, 2003). During this final high-risk period, individuals often exhibit pre-delusional unusual thoughts, pre-hallucinatory perceptual abnormalities, or pre-thought disordered speech (McGlashan, Miller & Woods, 2001).

This prepsychotic period is associated with a high rate of conversion to schizophrenia or another psychotic disorder. In one study, 62 treatment-seeking adolescents (mean age 16.4 years; range 12-22) were categorized into these three prodromal-period groups. Forty-seven percent of the adolescents who demonstrated severely attenuated positive symptoms (the period thought to be most proximal to psychosis) converted to a schizophrenia spectrum psychotic

disorder (schizophrenia or schizoaffective disorder) within one year (Cornblatt, Lencz, Smith, Correll, Auther & Nakayama, 2003).

As evidenced by the conversion rate demonstrated by this research, although prodromal criteria is the single best predictor of future psychosis (three- to four- fold higher than family history of schizophrenia), additional research is warranted to better understand the mechanisms of disease progression and highlight potential interventions to prevent or forestall development of a psychotic disorder (Cannon, 2008). One area of especially promising research is SU. Substance use during the prodrome is both common and associated with an increased conversion rate. One group of researchers examined 58 consecutively referred treatment-seeking patients; 29 met prodromal criteria (mean age 18.4, SD 4.8) based on the Structured Interview for Prodromal Symptoms (SIPS; McGlashan, Miller, Woods, Hoffman & Davidson, 2001) and 29 were classified as non-prodromal (mean age 19.2, SD 6.4). The prodromal individuals evidenced attenuated positive symptoms or brief intermittent positive symptoms. The most common comorbid diagnoses among the prodrome participants were major depressive disorder (59%) and substance use disorders (SUDs; 31%) followed by anxiety disorders (28%). Among the non-prodromal participants, affective disorders like depression were the most common (24%), followed closely by anxiety disorders (21%) and distantly by SUDs (14%; Rosen, Miller, D'Andrea, McGlashan & Woods, 2006). Another study found that individuals identified as exhibiting vulnerability to psychosis (based on SIPS scores) showed significantly more alcohol abuse and more commonly had a SUD than controls (Korkeila,

Svirskis, Heinimaa, Ristkari, Huttunen, Ilonen, et al., 2005). Researchers examining the conversion rate of at-risk individuals based on prodromal symptoms and/or family history found that of the 48 participants (mean age 18.6, S.D. 4.2) six (12%) converted to schizophrenia or another psychotic disorder within one year. Interestingly, of the 32 participants who reported no or minimal use of cannabis, 1 (3.2%) converted. In contrast, of the 16 participants who met criteria for cannabis abuse/dependence, 5 (31.3%) converted (Kristensen & Cadenhead, 2007). This result is consistent with other literature that indicates that the risk of developing schizophrenia and other psychotic disorders increases with heavier (Smit, Bolier, & Guijpers, 2004; Stefanis, Delespaul, Henquet, Bakoula, Stefanis, & Van Os, 2004; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002) and earlier use of cannabis (Arseneault, Cannon, Poulton, Murray, Caspi, & Moffitt, 2002).

Substance Use in Schizophrenia and other Psychotic Disorders

Prevalence and Incidence

There is a substantial body of literature on the relation between SU and psychiatric disorders, and much of this literature focuses on SU in general, rather than specific substances of abuse. The findings of this research will be reviewed, followed by a discussion of the research on specific substances.

Data from non-clinical samples of adolescents indicates a developmental trend towards increase in use. Researchers investigated use in 3072 community adolescents (12-18 years) and found that substance use increases linearly from early to late adolescence (Young, Corley, Stallings, Rhee, Crowley & Hewitt,

2002). Experimentation of nicotine, alcohol, and cannabis is virtually ubiquitous but disorders are less common. One in four adolescents meet criteria for abuse of at least one substance and one in five meet criteria for substance dependence.

The research on SU in general has consistently shown that lifetime history of SU is more prevalent in individuals exhibiting first episode psychosis and schizophrenia related disorders than in those from the general population (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002; Fowler, Carr, Carter, & Lewin, 1998; Soni, Jainer, Sridharan, Murthy, Kumar, Sickander, et al., 2005; Test, Wallisch, Allness, & Ripp, 1989; Van Mastrigt, Addington, & Addington, 2004). A study retrospectively assessed SUDs using both patients' self-reports and information from relatives in 232 individuals exhibiting first-episode psychosis. The researchers found that 24% of the patients abused alcohol prior to first admission, and 14% reported drug abuse; this is twice the rate seen in normal controls (Hambrecht & Hafner, 1996). Results from the Epidemiological Catchment Area (ECA) study conducted in the United States indicate a lifetime prevalence of SUD in schizophrenia of 47% (Reiger, Farmer, Rae, Locke, Keith, Judd & Goodwin, 1990). Other studies report rates of SUD in psychotic patients as high as 50–70% (Bell, Greig, Gill, Whelahan, & Bryson, 2002; Bromet, Schwartz, Fennig, et al., 1992; Drake, Osher, Noordsy, Hurlbut, Teague, & Beaudett, 1990; Mueser, Bennett, & Kushner, 1995; Westermeyer, 2006).

This discrepancy in prevalence may be due to several factors. First, there is evidence that previous studies of prevalence may underestimate use in participants with schizophrenia and other psychotic disorders. One study

examined 108 patients diagnosed with schizophrenia who had been consecutively admitted to a VA psychiatric inpatient unit. The researchers compared patient report of cocaine use to urine testing for cocaine use and found that a third of the participants who denied use had a positive urine test (Shaner, Khalsa, Roberts, Wilkins, Anglin & Hsieh, 1993). Second, patients with a dual-diagnosis may have impaired insight regarding the effect that substance use has on their illness. A study compared 164 participants with a dual-diagnosis of schizophrenia and SUD to 187 participants diagnosed with just a SUD on a measure of attitudes toward substance use problems. The results indicated that participants with a dual-diagnosis were less likely to identify themselves as having a substance problem (Jordan, Davidson, Herman, & BootsMiller, 2002). Together this research suggests that estimates of SUD in psychosis are significantly greater than that seen in the general population and that SUD rates may be higher than previous prevalence rates indicated.

There are also data to suggest that SU in persons suffering from a psychiatric illness is increasing. A prevalence study examined general medical research databases in England and Wales, and found that the comorbidity for psychiatric and SU disorders increased by 10% each year over the five-year period examined (1993-1998). The authors also found that comorbidity was being diagnosed in younger persons. Among patients with schizophrenia, the researchers saw a 128% increase in SU over the course of the study (Frisher, Collins, Millson, Crome & Croft, 2004).

Research also indicates that SU is elevated in persons identified as vulnerable to psychosis. That is, prodromal individuals show increased SUDs relative to healthy control subjects. Among persons identified as vulnerable to psychosis based on the SIPS and the Structured Clinical Interview for DSM-IV Axis I (SCID; First, Spitzer, Gibbon & Williams, 1997) there is significantly more lifetime SUD than observed in control subjects (Korkeila, Svirskis, Heinimaa, Ristkari, Huttunen, Ilonen, et al., 2005). Further, more severe positive and disorganized symptoms were found in vulnerable subjects with SUDs compared to subjects without a SUD. Another study found that SU decreased through the course of psychosis (Addington & Addington, 2007), suggesting that the prodromal and early stages of the illness may be periods of unique SUD vulnerability.

There is also evidence to suggest that the rate of SUDs is higher in patients with schizophrenia than in those with other disorders. Among inpatients with SUDs, 80% also had a comorbid schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, and schizophreniform disorder), compared with 63% with anxiety disorders, and 60% with mood disorders without psychosis (Swadi & Bobier, 2003).

The results of these studies suggest that SUDs are more prevalent in individuals exhibiting psychosis and a vulnerability to psychotic disorders than in those from the general population or those with other psychiatric disorders. The prevalence rates may be higher than originally thought (50-70%) and there

appears to be an increasing trend in substance use, especially among patients with psychotic disorders like schizophrenia.

The Relation of Substance Use with Symptom Profile and Course of Illness

Psychotic patients with SUDs evidence worse outcomes including poorer treatment compliance, housing instability and homelessness, medical problems, and more hospitalizations than psychotic patients without a SUD diagnosis (Dixon, 1999; Kavanagh, 2008; Margolese, Malchy, Negrete, Tempier, & Gill, 2004; Owen, Fischer, Booth, & Cuffel, 1996; Swofford, Scheller-Gilkey, Miller, Woolwine, & Mance, 2000). One study compared individuals with a SUD, individuals with a schizophrenia-spectrum disorder (i.e., schizophrenia, schizophreniform disorder, and schizoaffective disorder) and individuals with both a SUD and a schizophrenia-spectrum disorder. While all groups showed psychosocial problems, the dual diagnosis group evidenced the greatest risk for problems with occupation, housing, economics, and access to health care (Compton, Weiss, West, & Kaslow, 2005). A naturalistic 14-month follow-up of participants with first-episode schizophrenia showed that SU that persists after disease onset is associated with greater overall severity of illness compared to those who did not continue to use substances after disease onset (Harrison, Joyce, Mutsatsa, Hutton, Huddy, Kapasi, et al., 2008). In contrast, the patients who reported no lifetime SU manifested greater improvement in spatial working memory at follow-up when compared to those who either ceased SU after diagnosis or continued SU. That is, SU prior to clinical diagnosis was associated with more persistent cognitive deficits after clinical onset of schizophrenia, even

if the participant abstained from use after receiving a diagnosis. Another study compared in- and out- patients diagnosed with schizophrenia, 42 of whom abused substances and 45 of whom did not. The researchers found that participants who abused substances evidenced increased rates of hospitalization over a two-year period relative to participants who did not abuse substances (Cantor-Graae, Nordstrom, & McNeil, 2001).

There is also evidence that SUDs are associated with more severe positive symptoms through the course of psychosis. A meta-analysis of nine studies (n = 725) reporting Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) ratings in schizophrenia patients with and without SUDs found that those with a SUD manifested higher positive symptoms than those without a SUD (Talamo, Centorrino, Tondo, Dimitri, Henne, & Baldessarini, 2006). In a longitudinal study of 29 comorbid schizophrenia/substance abuse patients who were age and sex matched with 29 schizophrenia-only patients, more severe positive symptoms were evidenced at the first illness episode and at five yearly follow-up assessments in those who abused substances compared to those who did not (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002). Interestingly, recent evidence suggests that current use is associated with more severe positive symptoms than a history of use (Margolese, Malchy, Negrete, Tempier, & Gill, 2004). Outpatients (n = 207) diagnosed with a psychotic disorder (i.e., schizophrenia, schizoaffective, psychosis NOS, or delusional disorder) with a current dual-diagnosis (psychosis and SUD) evidenced significantly higher PANSS positive scores than lifetime dual-diagnosis or single

diagnosis (only psychosis). This suggests that the association between more severe positive symptoms and SUDs is at least partially temporally linked.

In contrast to the reports that SUDs are associated with worse overall outcomes and more severe positive symptoms, there is evidence that individuals with psychosis who use substances exhibit less severe negative symptoms. The longitudinal study of 29 comorbid schizophrenia/substance abuse patients who were age and sex matched with 29 schizophrenia-only patients found evidence of a non-significant trend toward lower SANS negative symptoms in substance abusers over the five-year follow-up period (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002). This trend was most pronounced in affective flattening. The difference between affective flattening ratings in the dual-diagnosis and single-diagnosis reached significance at the final fifth-year assessment. Supporting this finding, the meta-analysis of PANSS scores from nine studies cited above revealed that PANSS ratings in schizophrenia patients with a SUD manifested lower negative symptoms than those without a SUD (Talamo, Centorrino, Tondo, Dimitri, Henne, & Baldessarini, 2006).

The better negative symptom profile evidenced in subjects with both psychosis and a SUD may at first appear non-intuitive, however, this may be explained by superior social functioning as a means of obtaining substances. Negative symptom ratings include not only evaluations of affect but also social functioning. Studies examining SUD in psychosis consistently find levels of premorbid social functioning in those who use substances to be as good as or better than functioning in those who do not use substances. For example,

researchers compared those who did not use substances to those with a SUD, and found higher overall psychosocial functioning and higher scores on interpersonal relations (subscale of the Quality of Life Scale (QLS; Heinrichs, Hanlon, & Carpenter, 1984) in those with a SUD (Swartz, Wagner, Swanson, Stroup, McEvoy, McGee, et al., 2006). Only when the SUD involved cocaine did the overall psychosocial functioning of those with SUDs indicate lower functioning than that seen in non-users. Another study of 300 first episode psychosis participants found that fewer negative symptoms was associated with substance abuse as was better premorbid social functioning and more contact with friends in the last year (Larsen, Melle, Auestad, Friis, Haahr, Johannessen, et al., 2006). Researchers theorize that the reason for this discrepancy in premorbid function between psychotic patients with and without a SUD could be that while in the prodromal period, those with less severe negative symptoms have relatively preserved social functioning and therefore also have the means (i.e., contact with people) to acquire substances. There is also evidence that patients with a non-affective psychotic disorder like schizophrenia fare less well than others (intra- and inter-generationally) in occupational mobility (Wiersma, Biel, De Jong, Slooff, 1983; Samele, van Os, McKenzie, Wright, Gilvarry, Manley, et al., 2001). That is, despite higher educational attainment than their parents, fewer patients than would be expected given their cohort's success obtain or maintain employment. This downward drift in socioeconomic status of patients may also result in fewer monetary resources with which to obtain substances.

Alternatively, there could be something about the prodromal state of these individuals (other than preserved social functioning) that leads them to seek out substances. For instance, some researchers have found evidence of differences in reasons for use (i.e., self-reports of reasons for substance use are most commonly to alleviate symptoms, relieve boredom, or peer pressure; Dixon, Haas, Weiden, Sweeney, & Frances, 1990; Gearon, Bellack, Rachbeisel, & Dixon, 2001; Mueser, Bennett & Kushner, 1995; Test, Wallisch, Allness, & Ripp, 1989) or in personality traits (Mueser, Yarnold, Rosenberg, Swett, Miles & Hill, 2000).

A recent meta-analysis of associations between the Big Three and Big Five models (i.e., neuroticism, extraversion, disinhibition, conscientiousness, agreeableness, and openness) of personality traits and several disorders including SUDs (Kotov, Gamez, Schmidt, & Watson, 2010). The review included 175 studies published from 1980-2007 and reported elevated disinhibition and disagreeableness in adults with a SUD relative to those without a SUD.

Researchers have extensively studied the association between temperament, personality traits, and adolescent substance use. One study examined 170 adolescents at baseline and again 12-months later on personality measures and alcohol use (George, Connor, Gullo, & Young, 2010). The results indicate that psychoticism, extraversion, and novelty-seeking were the most powerful predictors of adolescent alcohol use. Other researchers that investigated adolescent substance use measured temperament in participants at four months and risk-taking during adolescence and found that high risk-taking and high behavioral inhibition predicted later substance-related behavior problems

(Williams, Fox, Lejuez, Reynolds, Henderson, Perez-Edgar, et al., 2010). Another prospective study examined a twin sample at 17 years old and again 3 years later (Elkins, King, McGue, Iacono, 2006). Lower constraint was associated with substance use disorders at 17-years-old than was seen in those who evidenced substance use disorders at 20-years-old. High negative emotionality was related to either age of onset.

Together, these traits suggest a personality profile that might indicate high risk for developing a substance use disorder. Studies indicate that willingness to take risks (novelty-seeking and high risk-taking), a propensity to act (disinhibition and low constraint), and negative emotions (disagreeableness, high negative emotionality, psychoticism; McCrae and Costa, 1985) may predispose an individual to use substances. Researchers have linked high negative affect with measures of social anhedonia in schizophrenia (Blanchard, Horan, & Brown, 2001).

In a seminal article, Shedler and Block (1990) longitudinally studied adolescents from preschool through age 18. At ages 7, 11, and 18 there were differences between the groups who abstained, experimented, or used frequently. They found that adolescents who engaged in some experimentation were the healthiest (e.g., better social skills, impulse control, and emotional experience and expression). Those who used drugs frequently endorsed interpersonal alienation, poor impulse control, and manifested emotional distress. Adolescents who had never experimented with any drug by age 18 were anxious, emotionally

constricted, and lacked social skills. This research suggests that maladjustment may precede substance abstinence or abuse/dependence.

It should be noted that some investigations have not revealed an association between symptom severity and SUDs. The research designs of the studies varies between examination of participants diagnosed with current SUDs and those with a history, but not current, SUDs; other researchers combine participants with current SUDs and those with a history of SUDs. These methodological discrepancies may lead to greater variability in results as differences have been found between the symptom presentations of those with a history of SUDs compared to current SUDs. Further, the studies that fail to find an effect generally examine more chronic, older participants (late 30s) than studies that find an association between symptom severity and SUDs, which usually include less chronic, younger participants (participants in their 20s). This is consistent with evidence that drug abusers, those with and those without psychosis, are generally younger (i.e., under 30 years of age; Hambrecht and Hafner, 1996; Rabinowitz et al., 1998; Regier et al., 1990; Van Mastrigt, Addington, & Addington, 2004).

Examining studies in light of these factors suggests possible moderators of the relationship between SUDs and symptoms. In one study, 172 participants with schizophrenia (mean age 32.8 +/- 7.65 years, range 18-54 years) and a diagnosis of either alcohol or cannabis use disorder revealed only a trend for more severe symptoms to be associated with substance abuse (Brunette, Mueser, Zie, & Drake, 1997). The age of the participants may have influenced the results. Another study

examined 40 age-, sex-, and race-matched participants diagnosed with psychosis (schizophrenia or schizoaffective disorder) with and without SUDs (the 20 participants with SUDs had a mean age of 38.95 +/- 7.54 years, the 20 participants without SUDs had a mean age of 39.40 +/- 7.67 years; Scheller-Gilkey, Tomas, Woolwine & Miller, 2002). The authors found no differences between the groups in positive, negative, or generalized symptoms. It is possible that the older age of the participants influenced the findings as well. Another study compared 25 schizophrenia outpatients with SUDs and 30 participants with a single-diagnosis of schizophrenia. If the participant did not meet DSM-IV criteria for a SUD in the last six months the participant was classified as a non-substance-user. The mean age of the participants was 39 years (+/- 7.42). The researchers reported no difference in psychiatric symptoms as a function of SU (Gearon, Bellack, Rachbeisel, & Dixon, 2001). Again, the older age of the participants and the lack of classification of history of SUD may have influenced the results.

These findings suggest that age or the early course of the illness may be a moderator of the relation between substance use and symptom severity. However, other results suggest that the age of participants and history of use are less important than the current level of substance use. Researchers examined 147 outpatients with psychosis (schizophrenia or schizoaffective disorder) and found that those with both psychosis and a current SUD evidenced higher overall symptoms at baseline compared to those with a lifetime SUD or no history of a SUD (Margolese, Negrete, Tempier, & Gill, 2006). The mean age of the group

(36.2 +/- 10.9 years) could be considered older. Thus, in this study, recency of use appeared to "trump" the age of the users and having a history of use. Therefore, both recency of use and age may be important factors in understanding the complex relationship between SUDs and symptom presentation.

Conclusions

In summary, the demographic pattern of substance use among patients with schizophrenia and other psychotic disorders appears to parallel that of the general population (male gender and younger age are associated with use), however, persons with psychosis are at least two-times more likely than those in the general population to report lifetime use. Further, the prodromal period and the early years of the illness may be a time of increased substance vulnerability, in terms of both prevalence of use and the effect of the substances on the disorder.

As described above, cross-sectional and longitudinal studies indicate that SU by patients is associated with a worse prognosis and poorer occupational function. There is also some evidence that SU is linked with more severe positive symptoms. In contrast, however, it appears that schizophrenia patients with SU are characterized by *less* severe negative symptoms and better social functioning, particularly early in the illness. It is likely that the differential association of SU with positive and negative symptoms reflects the behavioral characteristics typically required for access to substances. Thus, patients and prodromal individuals with more pronounced social withdrawal and affective deficits would be less likely to be in the social situations where substances are obtained and used.

Although the literature that addresses nonspecific SU in schizophrenia has contributed to our understanding of the link between SU and patient demographics, symptoms and illness course, it does not shed light on the relationship between specific substances and psychosis. Yet, the type of substance may be a significant factor determining the relation of SU with the phenomenology and course of psychosis. Alcohol and cannabis are the most commonly used and abused substances among psychiatric patients (Kavanagh, Waghorn, Jenner, Chant, Carr, Evans, et al., 2004; Mueser, Yarnold, Levinson, Singh, Bellack, Kee, et al., 1990). Given the different chemical profiles of these substances, it is possible that they are associated with different symptom profiles and illness course (this may, in part, account for some of the discrepancies in reported findings of the effects of SU on psychosis). In the sections below, research focusing on the relation of schizophrenia and other psychotic disorders with alcohol and cannabis use, respectively, will be reviewed.

Alcohol Use and Psychotic Disorders

First, the prevalence and incidence of alcohol use is established. Then, the relation between alcohol and psychosis will be examined in terms of symptoms and the disease course (i.e., age of onset, symptom profile, course of illness after diagnosis), and age will be examined as a potential moderator. In addition, evidence of a dose-dependent relationship and specificity of these findings to alcohol and to schizophrenia and other psychotic disorders will be reviewed. Finally, potential mechanisms of action will be explored. The same framework

will be used for the examination of the relation between cannabis and schizophrenia.

Prevalence and Incidence

The most common drug of choice for schizophrenia patients is alcohol, and alcohol use disorders (AUDs) are the most common comorbid disorders in schizophrenia (Brady, Casto, Lydiard, Malcolm, Arana, 1991; Cantor-Graae, Nordstrom & McNeil, 2001; Drake & Mueser, 2002; Fowler, Carr, Carter & Lewin, 1998; Swofford, Kasckow, Scheller-Gilkey, & Inderbitzin, 1996). Interestingly, persons with schizophrenia often evidence alcohol-related problems without meeting criteria for a disorder, that is, without alcohol dependence or abuse (Drake & Wallach, 1989; Drake, Osher, Noordsy, Hurlbut, Teague, & Beaudett, 1990; D'Souza, Abi-Saab, Madonick, Forselius-Bielen, Doersch, Braley, et al., 2005). This suggests that use, in addition to abuse and dependence, should be examined in persons with schizophrenia and other psychotic disorders. However, the majority of published reports focus on patients with AUDs, and relatively few address just alcohol use.

Approximately 28% to 47% of patients with schizophrenia or another psychotic disorder are dependent on or abuse alcohol (Addington & Addington, 2007; Cantor-Graae, Nordstrom & McNeil, 2001; Kavanagh, Waghorn, Jenner, Chant, Carr, Evans, et al., 2004; Mueser, Yarnold, Levinson, Singh, Bellack, Kee, et al., 1990). Although estimates vary, the general trend in the published data suggests that nearly half of schizophrenia patients who use alcohol begin to do so before the onset of the disease (Buhler, Hambrecht, Loffler, an der Heiden &

Hafner, 2002; Cantor-Graae, Nordstrom & McNeil, 2001; Dixon, 1999). In addition, one study found that AUDs are more pronounced in the first year following onset of psychosis than in the subsequent two years (Addington & Addington, 2007), which would suggest that the prodrome and the early stages of the illness are times of increased vulnerability to alcohol use.

Misuse of alcohol among psychosis patients has been associated with a variety of clinical and demographic characteristics including male sex, younger age, earlier age of onset, lower educational functioning, better social functioning, and cannabis use (Addington & Addington, 2007; Solter, Thaller, Bagaric, Karlovic, Crnkovic, & Potkonjak, 2004; Walker, Bettes, Kain, & Harvey, 1985). Also, an increased likelihood of comorbidity (e.g., mood and anxiety disorders) is associated with AU (Cuffel & Chase, 1994; Duke, Pantelis, & Barnes, 1994; Kirkpatrick, Amador, Flaum, Yale, Gorman, Carpenter, et al., 1996). These potential moderators, in tandem with the proposed criteria for better characterizing the potential causal relationship between SU and psychosis, including a relation of SU with the course or profile of symptoms, a dose-dependent relationship, temporality, that is, evidence of use prior to onset of the disease or symptom exacerbation, and empirical or theoretical evidence for potential mechanisms of action (Arseneault, Cannon, Witton & Murray, 2004; Thornicroft, 1990) provide a framework for the examination of the literature.

The Relation of Alcohol Use with Symptom Profile and Course of Illness

Patients presenting with both a psychotic disorder and an AUD appear to have a worse prognosis. In a two-year retrospective chart study of 262 outpatients,

researchers found that participants using alcohol required significantly more hospitalizations than those not using any substances (Swofford, Scheller-Gilkev, Miller, Woolwine & Mance, 2000). In dual-diagnosis patients (AUD and psychosis), researchers often find poor compliance with psychopharmacotherapy, higher rate of hospitalization, longer hospital stays, and higher number of relapses (often defined as recurrence or exacerbation of positive symptoms, rather than negative symptoms; Cantor-Graae, Nordstrom & McNeil, 2001; Cuffel & Chase, 1994; Dixon, 1999; Gerding, Labbate, Measom, et al., 1999; Solter, Thaller, Bagaric, Karlovic, Crnkovic, & Potkonjak, 2004; Soni & Brownlee, 1991). A prospective study that examined 232 first episode participants over a five-year period also found that those using substances evidenced a worse outcome, as indexed by treatment compliance, use of rehabilitation services, and employment status (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002). Treatment noncompliance is associated with a worse outcome (rehospitalization; Green, 1988) and is an impediment to preventing relapse. A review of seven studies examining the relapse rates in placebo compared to antipsychotic groups found that 73% of patients who suffered clinical exacerbation and required hospitalization did not comply with the treatment prescribed (Ayuso-Gutierrez & DelRio-Vega, 1997). The detrimental effects of AUDs on outcome appear to occur in a dose-dependent pattern. A one-year prospective follow-up study on 75 rural outpatients with schizophrenia found that as AU increased, so did unstable housing, conceptual disorganization, denial of mental illness, and rehospitalization (Osher, Drake, Noordsy, Teague, Hurlbut, & Biesanz, 1994).

Although the studies examining AU and psychosis are few, some have found evidence that AU is associated with increased positive symptoms. One study examined 53 schizophrenia and other psychotic disorder outpatients who used alcohol and were age- and sex-matched with 53 psychotic patients who did not use alcohol. The researchers found that those using alcohol evidenced significantly higher scores for hallucinations and a trend toward higher scores for delusions (Duke, Pantelis, & Barnes, 1994). Other studies have found similar results (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002; Fowler, Carr, Carter, & Lewin, 1998).

Similar to the profile shown in studies that examined persons with psychosis and general SU, participants with psychosis and AU may evidence better social functioning than persons with only a psychosis disorder. One study compared 34 past alcohol abusers to 17 abstainers (never consumed more than 5 drinks, never consumed more than 3 consecutive days, never experimented with any other drugs of abuse) who had been diagnosed with schizophrenia. The abstainers evidenced worse social functioning than the abusers (Zisook, Heaton, Moranville, Kuck, Jernigan, & Braff, 1992). Another study found that among 83 inpatients with a schizophrenia spectrum disorder (schizophrenia, schizoaffective, schizophreniform), past and current alcohol users evidenced fewer negative symptoms and better sexual adjustment during adolescence than those who did not use alcohol (Dixon, Haas, Weiden, Sweeney, & Frances, 1991).

Together these studies suggest that alcohol use is common in persons with a psychotic disorder. In fact, several studies find that it is the most commonly

used substance among persons with schizophrenia or another psychotic disorder. AU is associated with a poorer outcome. There is evidence suggesting that this relationship may follow a dose-dependent pattern such that more use is associated with a worse outcome than less or no use. AU is also associated with higher ratings on positive symptom scales and some researchers have also found that AU is associated with better social functioning and thus lower negative symptom scores.

There is evidence to suggest specificity of these findings to alcohol. One study compared patients who use alcohol to those who use illegal drugs (e.g., cannabis and narcotics) and found that schizophrenic patients with AUDs and patients diagnosed with only schizophrenia were better socially adjusted than those with schizophrenia who use illegal substances (Modestin, Gladen, & Studer, 2001). Another group of researchers found that participants with schizophrenia who use alcohol had fewer negative symptoms than those who use other substances (Swofford, Scheller-Gilkev, Miller, Woolwine & Mance, 2000).

This relation could reflect preferential use (e.g., persons with fewer negative symptoms are more likely to use alcohol because the individuals have social contacts so alcohol can be procured, and the known depressant effects of alcohol are more tolerable) or a causal relationship (e.g., the effect of alcohol on neurotransmitter levels influences positive symptoms). Further, pre-existing vulnerabilities could be triggered or exacerbated by SU making those with a predisposition to psychosis who also use substances more likely to develop schizophrenia. Similarly, those with pre-existing vulnerabilities could be more

likely to use substances. Age of use could also influence the relationship between SU and schizophrenia. For example, it is possible that use at age 30 would not trigger underlying vulnerabilities while use at age 15, when the brain is still developing and is therefore more vulnerable to insult, could exacerbate prodromal symptoms and lead to early and/or more severe psychosis than would be evidenced without SU.

Potential Mechanisms

Chronic AU in nonpsychiatric populations has consistently been related to frontal lobe dysfunction and memory deficits (i.e., deficits associated with Korsakoff's syndrome). Specifically, faulty glutamatergic, cholinergic, muscarinic, and dopaminergic neurotransmittion has been associated with AU (Potvin, Stip, & Roy, 2005). The role of sensitization has been highlighted in this process. Sensitization refers to a progressive influence on brain systems, such that chronic administration of equal or smaller doses induces stronger behavioral effects over time. Therefore, smaller doses of alcohol than might be considered abuse or dependence in a normal population, may adversely affect an already vulnerable glutamatergic, cholinergic, muscarinic, and/or dopaminergic neurotransmitter system, thereby increasing risk in those with a predisposition to developing psychotic symptoms (Syed, Toshitaka, & Tomoji, 2004).

Alcohol's impact on neurotransmitter activity could act in concert with pre-existing vulnerabilities to influence the age of onset and/or the course of schizophrenia. An additional risk factor may be alcohol use during adolescence. Alcohol use and abuse may have a more pronounced adverse effect on the

immature brain. Evidence of an interaction between the deleterious effects of alcohol consumption and adolescent brain development indicates that the protracted maturation of certain brain regions provides opportunities for stress and drugs to impinge upon trajectories of normal development (Kreek & Koob, 1998; Piazza & LeMoal, 1996), as adolescence is a period of heightened stress sensitivity and vulnerability to mental disorders (Walker, 2002). Brain areas and processes actively developing during adolescence include the prefrontal cortex, the hippocampus, white matter myelination, and gray matter pruning (Clark, Thatcher, & Tapert, 2008; Lenroot & Giedd, 2006; Spear, 2000). During this period of brain development, more than 40% of all synapses are eliminated through activity-dependent pruning of neuronal connections (Rakic, Bourgeois, & Goldman-Rakic, 1994; Huttenlocher, 1984). Given the extensive research on the vulnerability of postnatally developing brain areas, it is not surprising that there is mounting evidence that the hippocampus and prefrontal cortex may be susceptible to alcohol-induced dysmaturation.

Research shows a smaller hippocampal volume in adolescents with AUDs (De Bellis, Clark, Beers, Soloff, Boring, Hall, et al., 2000). It is possible that reduced hippocampal volume precedes alcohol use rather than results from alcohol use, therefore recent research has focused on the directional nature of the noted abnormalities. Researchers have used neural imaging to examine hippocampal volume in thirty-four matched youth at high- and low- risk for developing an AUD (based on a family history of alcohol abuse), prior to extensive alcohol use. The hippocampal volumes of the groups were comparable

(Hill, 2004). This suggests that the hippocampal volume decrease noted by DeBellis and colleagues (2000) was a result of alcohol exposure, rather than a phenotypical marker of alcohol abuse vulnerability. Another group of researchers compared people in their early twenties (at the end of this brain development period) to people in their late twenties on immediate and delayed recall tasks (Acheson, Stein, & Swartzwelder, 1998). Participants were tested under both placebo and alcohol (an amount equivalent to about 2-3 drinks was experimentally administered) conditions. Immediate and delayed memory results were similar for both groups in the placebo condition but the participants in their early twenties performed worse than those in their late twenties on both tasks after alcohol was administered. These imaging and neuropsychological results are consistent with the view that the hippocampus is sensitive to the acute, and possibly chronic, effects of alcohol exposure during adolescent brain development (White & Swartzwelder, 2004).

The prefrontal cortex is an area that undergoes relatively late maturation, with gray matter volumes decreasing over adolescence as white matter volumes increase (Lenroot & Giedd, 2006; Brown & Tapert, 2004). Adolescents with AUDs evidence white matter microstructure irregularities and brain response abnormalities during tasks requiring working memory (i.e., the prefrontal cortex), an area of impairment also associated with individuals with schizophrenia (Lewis, Cruz, Eggan, & Erickson, 2004). In addition, adolescents and adults with AUDs have been found to have smaller prefrontal white matter volumes (Agartz, Shoaf, Rawlings, et al., 2003; DeBellis, Narasimhan, Thatcher, Keshavan, Soloff, &

Clark, 2005; Krill, Halliday, Svoboda, & Cartwright, 1997). Performance on prefrontal cortex-mediated cognitive tasks progressively improves through childhood and adolescence (Diamond, 2002). The executive functioning associated with this brain region is not fully operational until at least age 21, suggesting that long-lasting impairments may result from alcohol use and other stressors experienced during adolescence (Thadani, 2002). Alternatively, immaturity of white matter development could represent a risk factor for the development of AUDs (Clark, Thatcher & Tapert, 2008). Further research is required to delineate the directional nature of the relationship between alcohol consumption and prefrontal cortex morphology and functioning.

Conclusions

Alcohol is the most commonly used and abused substance among persons diagnosed with schizophrenia and other psychotic disorders. There appears to be a trend towards more severe positive symptoms, yet less severe negative symptoms and better social functioning among patients who use alcohol. As mentioned above, the latter findings suggest that alcohol use, like SU in general, occurs in social contexts that are more accessible to patients that retain a higher level of social functioning. Nonetheless, despite the protection that better social functioning may confer, there is convincing evidence of a worse outcome (more hospitalizations, unstable housing, worse employment status) in patients who use alcohol.

What remains unclear, however, is whether alcohol use precipitates or worsens psychotic symptoms, or instead is used by patients to self-medicate

symptoms. To date, there is little evidence bearing on this question. Further, few studies have examined alcohol use by individuals who manifest signs of risk for psychosis. Recent evidence suggests that alcohol use during adolescence may represent an insult on normal brain development, which in turn may contribute instability to an already vulnerable system. In concert with these findings is growing evidence that suggests that cannabis use/abuse may contribute to the development of psychotic symptoms.

Cannabis Use and Psychosis

Prevalence and Incidence

Cannabis abuse (CA) is common in the US among persons with schizophrenia spectrum disorders and in prodromal youth. For example, regarding current use, a chart review study found that 42.8% of schizophrenia-spectrum (schizophrenia or schizoaffective disorder) adolescents currently met criteria for cannabis abuse (CA; Kumra, Thaden, DeThoma, & Kranzler, 2005). Studies of first-episode young adult patients have reported lower rates of CA including 12% (Margolese, Malchy, Negrete, Tempier, & Gill, 2004), 13% (Hambrecht & Hafner, 2000), and 23% (Sevy, Robinson, Holloway, Alvir, Woerner, Bilder et al., 2001). Even the lower estimates of 12-13% meeting criteria for CA is nonetheless double that seen in matched normal controls (Hambrecht & Hafner, 2000) and in the general population of 12th graders from 1976-2002 (Rey, Martin, & Krabman, 2004).

High rates of cannabis use (CU) by patients with severe psychiatric disorders are evidenced in other countries as well. A study conducted in an inner city area of the United Kingdom indicated that 43% of clients with severe mental health problems meet criteria for cannabis use disorders (CUDs; Graham & Maslin, 2002). Research conducted in Lebanon showed a similar rate (44.8%) of schizophrenia patients with a dual diagnosis of CUD (Karam, Yabroudi, & Melhem, 2002). It should be noted, however, that these urban rates likely exceed those that would be obtained with rural samples.

Lifetime use also appears to be higher in participants with, or at risk for, schizophrenia. In a sample of chronic male schizophrenic participants, 43% endorsed lifetime CU and 66.7% reported initiating use at least three years before onset of schizophrenia (Bersani, Olandi, Kotzalidis, & Pancheri, 2002). More recently, prospective studies of individuals who meet criteria for the prodrome to psychosis also revealed an elevated rate of CU. Furthermore, beginning use of cannabis in adolescence, that is, 18 years of age or younger and prior to the onset of schizophrenia, appears to confer increased risk (Arseneault, Cannon, Poulton, Murray, Caspi & Moffitt, 2002; Di Forti, Morrison, Butt, & Murray, 2007; Jockers-Scherubl, Wolf, Radzei, Schlattmann, Rentzsch, Gomez-Carrillo de Castro, et al., 2007; Semple, McIntosh, & Lawrie, 2005). Researchers report that of 29 prodromal participants, 17% endorsed a CUD, whereas none of the 29 non-prodromal participants endorsed a CUD (Rosen, Miller, D'Andrea, McGlashan, & Woods, 2006). There is also evidence that CU during the prodromal period for schizophrenia increased significantly, and disproportionately relative to other

psychiatric disorders, from 1965-1999 (Boydell, Van Os, Caspi, Kennedy, Giouroukou, Fearon, et al., 2006), indicating that this should be a growing concern for researchers interested in prevention of psychosis.

The Relation of Cannabis Use with Psychosis Onset

Within the past decade, mounting evidence from cross-sectional and longitudinal data have raised questions about the role of CU in triggering psychotic disorders, especially schizophrenia. In general, and often after controlling for socio-demographic factors, IQ, gender, and psychiatric diagnosis at baseline, researchers find that CU is associated with an increased risk for subsequently developing psychosis (Arendt & Munk-Jorgensen, 2004; Arseneault, Cannon, Witton & Muray, 2004; Degenhardt, Hall, & Lunskey, 2003; Zammit, Allebeck, Andreasson, Lundberg & Lewis, 2002). For example, a meta-analysis of six longitudinal studies from five countries concluded that regular CU by individuals in the general population predicted increased risk of psychosis (Degenhardt & Hall, 2006). Another meta-analysis that focused primarily on adolescent and young adult samples from birth, population, and conscription cohorts reported a pooled odds ratio of 2.1 (95% CI: 1.7-2.5) for developing psychosis after CU (Henquet, Murray, Linszen & van Os, 2005). In other words, the risk for developing psychosis was doubled in those with CU.

CU may interact with pre-existing vulnerability in predicting psychotic outcomes. One study that compared high- and low-risk youth found that those with baseline vulnerability for psychosis, as measured by sub-clinical symptoms, who also used cannabis were significantly more likely to be diagnosed with

psychosis at follow-up three years later than those who did not use cannabis (Verdoux, 2004). The author concluded that high-risk or vulnerable individuals are particularly sensitive to the effects of cannabis, resulting in an increased risk of presenting with clinical psychosis.

Beyond the increased risk of developing psychosis, it appears that lifetime CU is associated with an earlier age of onset of psychosis. One study of recent-onset schizophrenia patients obtained self-report data on drug and alcohol use and age at onset of psychosis (Barnes, Mutsats, Mutton, Watt, & Joyce, 2006). Results indicate that after controlling for use of alcohol and other substances, CU was associated with a younger age at onset of psychosis. Another study found that patients with CU and schizophrenia manifested an earlier age at first psychotic episode (Veen, Selten, van der Tweel, Feller, Hoek, & Kahn, 2004).

The Relation of Cannabis Use with Symptom Profile and Course of Illness

There is some evidence that the symptom profile of schizophrenia patients with CU differs from the symptom profile of other schizophrenia patients. A study that examined younger participants diagnosed with schizophrenia (mean age 15) who had been using for at least one year prior to the start of the study found that those with a CUD evidenced more and earlier psychotic relapses or exacerbations than those who did not use (Linszen, Dingemans, & Lenior, 1994). The results remained significant after controlling for antipsychotic medication dosage and adherence as well as other drug use (alcohol or other psychoactive substances). A prospective study that followed 101 patients with schizophrenia over 10 months found that CU predicted a significant increase in psychotic

symptoms (Degenhardt, Tennant, Gilmour, Schofield, Nash, Hall, et al., 2007). In contrast, when the authors examined the relation of CU with symptoms of depression, there was no relation, suggesting that the results were specific to psychotic symptoms. Further, psychotic and depressive symptoms at baseline did not predict use over the 10-month period of the study. Thus, it does not appear that CU was precipitated by symptoms, but instead the findings suggest a causal role of CU in exacerbating psychotic symptom severity (i.e., severity of symptoms at baseline did not predict cannabis use). Another follow-up study examined three groups of schizophrenia patients: those who were using cannabis during the six-month observation period, those who reported past use, and those who had never used cannabis (Negrete, Knapp, Douglas, & Smith, 1986). Those who reported using cannabis during the six-months of the study presented with significantly higher ratings of delusions and hallucinations at follow-up than those in the other two groups. A more recent study employed a similar design (Harrison, Joyce, Mutsatsa, Hutton, Huddy, Kapasi, et al., 2008). Researchers examined patient's lifetime use of cannabis, use at baseline, and use 14 months later. Those who continued to use over the follow-up period evidenced significantly more severe positive and depressive symptoms at follow-up, as well as greater overall severity of illness, but there was no relation between CU and negative symptom severity. Along the same lines, the Edinburgh High Risk Study (EHRS) revealed a significant relation of symptom severity in schizophrenia patients with frequency of cannabis use (Miller, Johnstone, Lawrie, & Owens,

2006). Taken together, these studies indicate that CU exacerbates psychotic symptoms after disease onset.

In contrast, as is the case with AU in schizophrenia, it appears that CU is associated with fewer negative symptoms and better premorbid adjustment (Arndt, Tyrrell, Flaum, & Andreasen, 1992; Compton, Furman, & Kaslow, 2004; Dixon, Haas, Weiden, Sweeney, & Fances, 1990; 1991; Mueser, Yarnold, Rosenberg, Swett, Miles & Hill, 2000). Again, it appears that when negative symptoms and social deficits are more severe, patients are less able to make the social connections that facilitate access to cannabis.

It should be noted that there is at least one report that showed no relationship between CU and positive and negative symptoms in schizophrenia. In a case register study of 757 cases of first-onset schizophrenia collected over four decades (1965-2004), researchers compared the 24% of the sample who reported using cannabis in the year prior to onset to the 73% who had not (3% were missing data; Boydell, Dean, Dutta, Giouroukou, Fearon & Murray, 2007). Controlling for age and gender, the logistic regression revealed no significant difference in symptom profile between cannabis users and non-users. Despite the impressive size of the database, several methodological concerns should be noted. First, the symptoms were assessed based upon the chart information and then rated on a separate instrument. Thus, the ratings used for this study were based upon psychiatrist ratings of chart information, not a compilation of direct ratings from a psychiatrist who had had contact with the patient. Second, the database was compiled over four decades. Recent evidence on the relative potency of

cannabis (e.g., THC content) suggests that cannabis used in the 1960s and 1970s have fewer adverse effects compared to the cannabis used in the 1980s and 1990s, upon which most studies with positive findings are based (ONDCP, 2009). These methodological concerns should not completely discount the presence of a null finding, rather, this should provide impetus for replication and further exploration of potential mediators and moderators of the relationship between cannabis and the symptomological presentation of psychosis.

In addition to the data suggesting a relationship between CU and symptom profile and course, there is also evidence of a relation between CU and other indices of outcome in schizophrenia. One study found that the schizophrenia patients who reported using cannabis during the six-month period of a prospective study had a higher average number of hospital visits than those who reported past use or no use (Negrete, Knapp, Douglas, & Smith, 1986). Another follow-up study found that first-episode schizophrenia patients who reported no lifetime substance use showed greater improvement in spatial working memory 14 months later than those who reported using cannabis in the past (Harrison, Joyce, Mutsatsa, Hutton, Huddy, Kapasi, et al., 2008). Poor course, defined as continuous psychotic illness or a score of less than 39 on the Global Assessment of Functioning scale (GAF; DSM-IV-TR), was the outcome measure in a recent follow-up study (Selten, Veen, Hoek, Laan, Schols, van der Tweel, et al., 2007). Participants diagnosed with schizophrenia were examined 30 months after first contact with a physician, and CUD during the follow-up period was among the best predictors of poor course. One five-year follow-up study compared

schizophrenic patients with current CU to a control group matched on age, gender, and year of admission (Caspari, 1999). The researcher reported that patients with a previous CUD evidenced significantly more hospitalizations, worse psychosocial functioning, and higher scores on measures of thought disturbance and hostility.

A few studies show no relation of cannabis use with outcome. One group of researchers examined participants with schizophrenia alone, schizophrenia and CUDs, and no mental disorder on measures of cognition and decision-making and found no difference between the two schizophrenia groups (Sevy, Burdick, Visweswaraiah, Abdelmessih, Lukin, Yechiam, et al., 2007). Another study examined 57 people with schizophrenia who reported substance misuse and found no relationship with outcome measures (e.g., number of admissions to hospital, housing, employment, or marital status; Duke, Pantelis, McPhilips, & Barnes, 2001).

One possible explanation for the apparent inconsistency in results is the finding that, in one group of schizophrenia patients, cognitive functioning was better among those who reported a history of CUD earlier in the course of illness (Coulston, Perdices, & Tennant, 2007). One cross-sectional study compared participants with and without schizophrenia and/or CUD (Jockers-Scherubl, Wolf, Radzei, Schlattmann, Rentzsch, Gomez-Carrillo de Castro, et al., 2007). Persons with schizophrenia performed worse on cognitive tasks than healthy participants, but those with schizophrenia and a CUD *prior* to their first episode of psychosis evidenced better neuropsychological functioning. This effect was more

pronounced when the CUD began before age 17. A follow-up study of patients 10-12 years after their first-episode of psychosis found no significant differences between those who used cannabis prior to onset and those who did not on measures of clinical and behavioral functioning (Stirling, Lewis, Hopkins, & White, 2005). The researchers found a difference in cognitive functioning such that patients who had used cannabis evidenced better cognitive functioning than those who had not used cannabis. Corroborating these findings, Potvin, Joyal, Pelletier & Stip (2008) conducted a meta-analysis of 23 studies including data from 1807 persons with schizophrenia. The results indicated that when the type of substance used and the mean age of the participants at assessment were taken into account, cannabis use was associated with higher scores in problem solving and reasoning as well as verbal memory, and that current age was inversely related to the size of the effects. In other words, the younger the subjects the stronger the positive relation between CU and cognitive function. These relations may, again, reflect the social and cognitive resources that facilitate access to cannabis.

In summary, it appears that individuals who use cannabis prior to onset, or early in the course of their disorder may be less cognitively impaired than other schizophrenia patients. This is consistent with findings that patients with CU show less severe negative symptoms and social impairment early in the course of their illness. However, as described above, the studies of CU and long-term course often suggest that CU is associated with poorer prognosis, as indexed by relapse and rehospitalizations. Thus, the recency and extent of CU may impact results and contribute to discrepancies noted in the extant literature.

Experimental Studies of the Effects of Cannabis (Δ^9 THC) on Patients and Healthy Controls

The results of several experimental studies provide evidence suggesting a neural mechanism underlying the relation between CU and psychosis. In order to directly test the effect of cannabis on psychotic symptoms and cognitive performance, several research groups have examined the effects of the active psychotropic agent in cannabis, Δ^9 tetrahydrocannabinol (abbreviated as Δ^9 THC or THC), on both schizophrenia patients and healthy participants.

The research on healthy participants indicates acute induction of positive and negative symptoms when Δ^9 THC is experimentally administered (Bhattacharyya, Fusar-Poli, Borgwardt, Martin-Santos, Nosarti, O'Carroll, et al., 2009; D'Souza, Braley, Blaise, Vendetti, Olivery, Pittman, et al., 2008; D'Souza, Perry, MacDougall, Ammerman, Cooper, Wu, et al., 2004; Sewell, Ranganathan, D'Souza, 2009). Positive symptoms such as suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and fragmented thinking are among the most common. Negative symptoms such as blunted affect, lack of spontaneity, apathy, social and emotional withdrawal, impaired memory, and impaired attention are also often noted.

Cognitive functioning is also affected by Δ^9 THC administration in healthy participants. Δ^9 THC, a cannabinoid, binds to endogenous cannabinoid (endocannaabinoid) receptors in the brain (CB1 receptors) and other areas of the body (e.g., gut and spleen; CB2 receptors). CB1 receptors evidence high densities in the basal ganglia, cerebral cortex, and hippocampus (Herkenham, Lynn, Little,

Johnson, Melvin, de Costa, et al., 1990). The location of these receptors suggests cannabinoid involvement in attentional and memory processes (Roser, Juckel, Rentzsch, Nadulski, Gallinat, & Stadelmann, 2008). Consistent with this theory, the most robust findings on the acute cognitive effects of Δ^9 THC indicate deficits in verbal memory retrieval and attention in healthy participants. One group of researchers found that Δ^9 THC impaired verbal free recall, but recognition recall was less disrupted, suggesting that Δ^9 THC effects act primarily on verbal working memory and retrieval more than encoding (D'Souza, Perry, MacDougall, Ammerman, Cooper, Wu, et al., 2004). Other researchers who found similar results in healthy participants during a functional magnetic resonance imaging study (fMRI) noted that a decrement in parahippocampal response during encoding was directly correlated with recall score on a verbal paired associate learning task (Bhattacharyya, Fusar-Poli, Borgwardt, Martin-Santos, Nosarti, O'Carroll, et al., 2009). However, these healthy participants under the influence of Δ^9 THC group did not demonstrate the normal linear decrement in activation. This suggests that Δ^9 THC influences the functioning in the parahippocampal region, which is implicated in the pathogenesis of schizophrenia (Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). In addition, this finding may represent additional evidence for the role endogenous cannabinoids play in cognitive dysfunctions in schizophrenia (Roser et al., 2008).

Evidence implicating Δ^9 THC's role in attentional processes comes from electrophysiology and psychopharmacology research. The P300 is a brainwave component elicited by cognitive tasks that require attentional resource allocation

and active working memory (Polich, 1991). When compared to placebo, experimental administration of Δ^9 THC in healthy individuals is associated with a significant reduction of P300 amplitude (Roser, Juckel, Rentzsch, Nadulski, Gallinat, & Stadelmann, 2008). Reduced amplitude of the P300 wave in participants with schizophrenia is a consistent finding (e.g., Braff, 1993; Papageorgiou, Oulis, Vasios, Kontopantelis, Uzunoglu, Rabavilas, et al., 2004) and is often linked to the impaired attention and working memory evidenced in schizophrenia patients (Iversen, 2003; Ranganathan & D'Souza, 2006; Solowij, 1998). In a 2-test-day double-blind study, researchers administered haloperidol at a dose expected to produce antipsychotic effects and presumed to act relatively selectively as a dopamine receptor (DA D2) antagonist (0.057 mg/kg, equivalent to 4 mg in a 70-kg individual; D'Souza, Braley, Blaise, Vendetti, Olivery, Pittman, et al., 2008). Participants included healthy volunteers as well as volunteers who reported frequent cannabis use. On one of the test days, following haloperidol administration, participants were given Δ^9 THC. Δ^9 THC significantly impaired recall and attention. Interestingly, haloperidol further worsened Δ^9 THC-induced recall deficits. Both haloperidol and Δ^9 THC worsened distractability and vigilance. This suggests not only an interaction between dopaminergic and cannabinoidergic systems but is consistent with previous findings from an experimental study showing Δ^9 THC-exacerbation of psychotic symptoms in schizophrenia patients on antipsychotics like haloperidol (D'Souza, Abi-Saab, Madonick, Forselius-Bielen, Doersch, Braley, et al., 2005). This may represent a limit to the relevance of the cannabinoid model of psychosis but may also be a

candidate explanation for the positive symptoms that are resistant to DA D2 receptor antagonist antipsychotic drugs (D'Souza et al., 2008).

Specificity of Cannabis Use to Schizophrenia

One longitudinal study compared first-admission patients with schizophrenia to patients with affective psychosis (Kovasznay, Fleischer, Tanenberg-Karant, Jandorf, Miller, & Bromet, 1997). The results showed that participants with schizophrenia were more likely to use cannabis than those with affective psychosis. Lifetime history of SU in schizophrenia patients was associated with worse clinical functioning at the six-month follow-up. The same results were not seen in patients with affective psychosis. In addition, evidence has been found that suggests that CU during the prodromal period to psychosis increased significantly, and disproportionately, relative to other psychiatric disorders, from 1965-1999 (Boydell, Van Os, Caspi, Kennedy, Giouroukou, Fearon, et al., 2006). Therefore, evidence suggests a more pronounced increase in CU among individuals who subsequently develop schizophrenia.

Potential Mechanisms: Cannabinoids and Dopamine

There are several potential neural mechanisms that would account for a positive relation between CU and psychosis. Of the eight major cannabinoids in cannabis, two have been explored enough to contribute to our understanding of the effects of cannabis. Cannabidiol, a non-psychotropic cannabinoid, is associated with anti-convulsant, anti-nausea, anti-inflammatory, and anti-anxiety properties (Castle & Murray, 2004). Δ^9 THC has been shown to have a myriad of effects on the brain. The best-known endogenous cannabinoid, anandamide,

exhibits many of the properties associated with Δ^9 THC (Devane, Hanus, Breuer, Pertwee, Stevenson, Griffin, et al., 1992). Cannabinoids bind to endogenous cannabinoid (endocannabinoid) receptors in the brain (CB1 receptors) and other areas of the body (e.g., gut and spleen; CB2 receptors). Evidence for the roll of CB1 receptors in the effects of cannabis has been shown experimentally with administration of CB1 receptor blockers to participants; those who received a CB1 receptor blocker reported a reduced effect of cannabis (Huestis, Gorelick, Heishman, Preston, Nelson, Moolchan, et al., 2001).

Cannabinoid receptors are primarily located on axons and nerve terminals (presynaptic). This is consistent with the hypothesis that cannabinoids act through modulation of neurotransmitter release. The highest densities of CB1 receptors are found in the frontal regions of the brain, the basal ganglia, cerebellum, hypothalamus, anterior cingulate cortex, and the hippocampus. It is believed that endocannabinoids are integral to the modulation of synaptic transmission by causing inhibitory effects of both excitatory and inhibitory neurotransmitter release (Castle & Murray, 2004). Exogenous cannabinoids mimic this activity; their overall effect is to cause persistent inhibition of neurotransmitter release from the nerve terminals that express CB1 receptors. Thus, exogenous cannabinoids interrupt the modulation activity of endocannabinoids. Experimental studies have shown that Δ^9 THC inhibits the release of a number of neurotransmitters including acetylcholine, γ-aminobutyric acid (GABA), noradrenaline (norepinephrine), dopamine, and 5-hydroxytryptamine (5-HT;

Katona, Sperlagh, Magloczky, Santha, Kofalvi, Czirjak, et al., 2000; Schlicker & Kathmann, 2001).

Dopamine D2 receptor agonists are associated with an increase in anadamide synthesis and release in the striatum (Giuffrida, Parsons, Kerr, Rodriguez de Fonseca, Navarro & Piomelli, 1999). That is, agents that preferentially bind to D2 receptors cause anadamide to be released into the striatum, leading to greater inhibition of neurotransmitter release. Thus, an excess of dopamine influences endocannabinoids and is associated with lower levels of other neurotransmitters. Two proposed effects of the resulting decrease in neurotransmitters are impairment of short-term memory via the inhibition of the release of GABA and glutamate in hippocampal circuits and a reduction in levels of glutamate needed to activate N-methyl-D-aspartate (NMDA) receptors, which are required for the vital learning process known as long-term potentiation (LTP; Castle & Murray, 2004).

It has been proposed that exogenous cannabinoids, like Δ^9 THC, have a similar effect on the brain as excess dopamine. Dopamine is thought to be significantly associated with psychotic symptoms (dopamine agonists elicit symptoms and antipsychotics block dopamine receptors; Davis, Kahn, Ko, & Davidson, 1991; Lieberman, Perkins, Belger, Chakos, Jarskog, Boteva, et al., 2001). There is evidence to suggest that Δ^9 THC causes dopamine release in the nucleus accumbens and the prefrontal cortex (Gardner & Lowinson, 1991; Tanda, Pontieri, & Chiara, 1997). Lending additional evidence to the parallels between the effects of cannabis and schizophrenia on the brain are findings of marked

elevation of endocannabinoid levels in the cerebrospinal fluid of people with schizophrenia (Leweke, Giuffrida, Wurster, Emrich, Piomelli, 1999). There is documentation of an eight-fold increase in anandamide in antipsychotic-naïve first-episode participants (Sundram & Castle, 2007). Furthermore, researchers have found increased densities of the CB1R in schizophrenia (post-mortem brain tissue studies) in the prefrontal cortex (Dean, Sundram, Bradbury, Scarr, & Copolov, 2001) and anterior cingulate cortices (Zavitsanou, Garrick, & Huang, 2004). The parallels noted here suggest that there are similarities between the effects of schizophrenia and Δ^9 THC on neurotransmitter modulation.

Diathesis-Stress and Adolescent Brain Development

Substance use in adolescence is of particular concern because research has indicated that adolescence is a period of heightened stress sensitivity and vulnerability to a number of mental disorders (Spear, 2000; Walker, 2002; Walker and Diforio, 1997). This vulnerability is likely a result of a complex series of events. Recent research on development of the frontal lobe and neurotransmitters systems elucidates potential processes. Cholinergic, serotonergic, and dopaminergic systems continue to develop into early adulthood (Benes, 2001). Developmental periods are often associated with vulnerability because developing systems may be uniquely sensitive to environmental and behavioral events. Normal human brain development, particularly during adolescence, entails pruning of neural pathways. Further, the prefrontal cortex continues to form into adolescence and early adulthood, suggesting that the continued growth and maturation of monoaminergic systems may contribute to the formation of mature

cognitive abilities mediated by this region (Goldman-Rakic, Bourgeois, and Rakic, 1997; Benes, Taylor, and Cunningham, 2000).

There is evidence that the adolescent brain may be more sensitive to the adverse effects of substances than the mature brain. For example, in one study, participants were administered Δ^9 THC and then assayed for brain-derived neurotrophic factor (BDNF), a neurotrophin involved in the regulation of the genesis, differentiation, survival, and repair of neurons (Binder & Scharfman, 2004; Chao, Rajogopal, & Lee, 2006). This exposure to Δ^9 THC increased BDNF levels in healthy controls but not light users of cannabis (defined as lifetime exposure to cannabis greater than or equal to 100 times, recent cannabis exposure greater than or equal to ten times per month, cannabis use in the past week, positive urine toxicological test for cannabis at screening, met criteria for current cannabis abuse disorder). This suggests BDNF changes in cannabis-exposed brains and may be of importance for the developing brain and neurodevelopment disorders (like schizophrenia; D'Souza, Pittman, Perry, & Simen, 2009). There is also evidence that the endocannabinoid system is important in neurogenesis, neural specification, neural maturation and migration, axonal elongation, and glia formation, all of which are integral to neurodevelopment (Glave-Roperh, Aguado, Palazuelos, & Guzman, 2007).

In individuals with psychosis, there is evidence of excessive pruning of dopaminergic neurons that may lead to hypofrontality, likely as a result of interactions between the developing prefrontal cortex and cholinergic, serotonergic, GABAergic, and dopaminergic systems (Retaux, Besson, and Penit-

Soria, 1991; Benes, Taylor, and Cunningham, 2000). Hypofrontality, in turn, may lead to a reduction in mesocortical feedback and, therefore, a reduction in inhibition of the mesolimbic system (Milin, 2008). The mesocorticolimbic pathway is believed to play a role in the effects of stress (Kalivas & Stewart, 1991) and the onset of mental disorders is often associated with a precipitating stressful event (Norman & Malla, 1993). Thus, vulnerability and stress interact uniquely in the developing brain.

There is mounting evidence that cannabis use triggers an earlier trajectory of psychosis (Andreasson, Allebeck, Rydberg, 1987; Arendt & Munk-Jorgensen, 2004; Arseneault, Cannon, Witton & Muray, 2004; Degenhardt & Hall, 2006; Degenhardt, Hall, & Lunskey, 2003; Zammit, Allebeck, Andreasson, Lundberg & Lewis, 2002). This notion is based on findings that participants either at risk for psychosis (based on a genetic vulnerability or symptom ratings) or from the general population (e.g., large cohort studies and meta-analyses of general population research) who use cannabis appear to be at greater risk for developing psychosis. It is possible that this is a result of the interaction between vulnerability and increased stress sensitivity during adolescent brain development. It has been suggested that cannabis use should be regarded as a stressor that has the potential to precipitate the clinical occurrence of schizophrenia (Andreasson, et al., 1987). In support of this, research indicates that Δ^9 THC has been associated with increases in plasma cortisol, levels in healthy participants (D'Souza, Perry, MacDougall, Ammerman, Cooper, Wu, et al., 2004).

The hypothalamic-pituitary-adrenal (HPA) axis governs the release of cortisol, a glucocorticoid, by the adrenal gland. Cortisol is released by the HPA axis in response to stress, and negative feedback that modulates HPA activity is provided by glucocorticoids located throughout the brain. Further, cortisol release augments dopamine activity by increasing dopamine synthesis and receptor sensitivity (Walker & Diforio, 1997). Given that overactivation of dopamine pathways has been implicated in the etiology of schizophrenia, the augmentation of dopamine by cortisol suggests a mechanism for explaining the adverse effects of stress on schizophrenia (Walker, Mittal & Tessner, 2008). Thus, exposure to Δ^9 THC may trigger or potentiate psychotic symptoms via its effects on HPA activity and increases in cortisol secretion (D'Souza et al., 2004).

Conclusions

Current and lifetime CU has consistently been shown to be more common in persons at-risk for and diagnosed with schizophrenia than in the general population. CU is associated with an increased risk of developing psychosis, earlier age of onset, more severe positive symptoms, perhaps less severe negative symptoms, and, a general trend towards a worse prognosis. There is a dearth of studies examining the specificity of these effects to schizophrenia, and research on normal participants suggests that the psychotogenic effects of CU are not specific to patients with schizophrenia or other psychotic disorders. Finally, there is empirical and theoretical support for the assumption that developmental stage moderates the relation between CU and risk for psychosis, such that adolescents are particularly sensitive to the adverse effects of CU.

Goals of the Present Study

Based on the research findings reviewed here, it appears that both alcohol and cannabis use are associated with a less favorable prognosis for patients with schizophrenia and other psychotic disorders. Moreover, in the case of cannabis, there is evidence that it has the potential to trigger or exacerbate the positive symptoms of psychosis. This notion receives further support from experimental studies that have tested the effects of THC on symptoms and cognitive functions in both normal participants and schizophrenia patients.

To date, there has been little research on substance use or abuse in individuals at clinical risk for psychosis, particularly those who manifest prodromal signs. Further, there are no published reports on the independent and/or interactive effect of these substances. Such research is important because CU and SU are correlated in general and clinical populations (Drake & Wallach, 1989; Butler, Jenkins, & Braff, 1993).

Within the past decade, researchers have developed structured interview procedures for identifying prodromal syndromes, and this research has demonstrated that these subjects are at heightened risk for subsequent psychosis. For example, using the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2002; Miller et al., 2002), it has been demonstrated that 25 to 40% of individuals who meet criteria for the prodrome develop an Axis I psychotic disorder within 2 years (Woods et al., 2009).

In order to meet SIPS criteria for the prodrome, subjects must show one or more attenuated positive symptoms at a moderate level of severity, yet not at

levels of severity required for a diagnosis of a psychotic disorder. Thus, putatively prodromal individuals may report unusual ideas or perceptual experiences that are disturbing yet retain skepticism that the unusual ideations or sensory experiences are based in reality. Given the evidence that a substantial proportion of prodromal subjects show a progressive worsening of symptoms, often leading to psychosis, research on SU in this population holds promise for elucidating the relation between SU and symptom progression.

This research will examine both AU and CU in a prodromal sample, with the goal of testing the prediction that the use and/or abuse of these substances will be linked with current symptoms and the progression of symptoms. Both the independent and the interactive effects of AU and CU will be examined.

Hypotheses

The following hypotheses will be tested;

Hypothesis 1: There will be an inverse relationship between AU and negative symptoms at baseline. More specifically, better baseline social functioning will be associated with AU. This is based on the assumption that as impairment in social functioning decreases, the likelihood that the individual will be exposed to the social contexts that afford access to alcohol or encourage its use increases.

Hypothesis 2: There will be a positive and dose-dependent (i.e., no AU, AU, alcohol abuse (AA)/alcohol dependence (AD)) relationship between AU and

positive symptom severity at baseline and this effect will be partially independent of CU.

Hypothesis 3: There will be an inverse relationship between CU and negative symptoms at baseline. As with AU, this is based on evidence that social deficits impede access to recreational drugs.

Hypothesis 4: There will be a positive, dose-dependent (no CU, CU, cannabis abuse (CA)/cannabis dependence (CD)) relationship between CU and positive symptom severity at baseline and this effect will be partially independent of AU.

Hypothesis 5: There will be a positive relationship between AU at baseline and negative symptom severity at follow-up. There is evidence to suggest that an inverse relation of social function and negative symptoms may not persist throughout the follow-up period, as persistent AU is assumed to contribute to more severe functional deficits.

Hypothesis 6: There will be a positive, dose-dependent (no CU, CU, cannabis abuse (CA)/cannabis dependence (CD)) relationship between CU and positive symptom severity at baseline and follow-up, and this effect will be partially independent of AU.

Hypothesis 7: Age will be a significant moderator of the relation between CU and positive symptoms, such that younger age at baseline will be associated with a stronger relation between CU and symptoms at follow-up.

In addition to testing the above hypotheses, the present study will shed light on several important questions. The effects of alcohol and cannabis on the brain differ, and these differences may have implications for the nature of their relation with symptom severity and course. Both alcohol and cannabis likely have deleterious effects on the developing brain by acting on the hippocampus and the prefrontal cortex, however, cannabis also influences the basal ganglia, cerebellum, hypothalamus and the anterior cingulate cortex. Thus, the present study will help to elucidate the potential specificity of effects of AU and CU on prodromal symptom progression.

Method

Participants and Procedure

Participants (N=516 males, 372 females) were recruited at eight participating study sites as part of the North American Prodrome Longitudinal Study. Participants were typically interviewed in the morning to allow for collection of other data. Raters were mental health specialists and achieved agreement standards with other raters before conducting assessments. Reliability data was calculated based upon the post-training agreement of raters with the expert raters on the intensity of positive symptoms was in the excellent range both

across sites and within each site (overall = κ, 0.90; site-specific = κ range, 0.80-1.00**;** Cannon, Cadenhead, Cornblatt, Woods, Addington, Walker, et al, 2008).

Participants were assessed using the Structured Interview for Prodromal Syndromes (SIPS) and the Structured Clinical Interview for DSM-III-R (SCID-I; note: The SCID-I based upon DSM-III-R criteria were used to maintain consistency throughout the study, which began prior to publication of the SCID-I based upon DSM-IV criteria). This allowed for examination of symptoms, mood disorders, prodromal characteristics, and other diagnostic information. At baseline, the SIPS and SCID-I were administered and current substance use was assessed. The SIPS was administered again at the six-month follow-up.

For inclusion in the prodromal group, participants met all of the following criteria: understand and sign an informed consent (or assent for minors) document in English, meet diagnostic criteria for prodromal syndrome as per SIPS/COPS (see discussion below for specific SIPS/COPS criteria), the prodromal symptoms could not be better explained by an Axis I disorder, no current or lifetime Axis I psychotic disorder, no mental retardation, no past or current history of a clinically significant central nervous system disorder that could contribute to prodromal symptoms or confound their assessment, and no traumatic brain injury that included a severe concussion (Cannon, Cadenhead, Cornblatt, Woods, Addington, Walker, et al, 2008). For inclusion in the normal control group, participants met the following criteria: understand and sign an informed consent (or assent for minors) document in English, did not meet diagnostic criteria for prodromal syndrome as per SIPS/COPS, no mental retardation, no past or current history of a

clinically significant central nervous system disorder, and no traumatic brain injury that included a severe concussion.

A total of 888 participants participated in the study; the subsample included in the present study varied depending upon the cross-sectional or longitudinal nature of the data analyses. Cross-sectional hypotheses were tested utilizing the participants (N=710) for whom baseline symptom data and substance use data were complete and who met criteria for the prodrome based on the presence of Attenuated Positive Symptom Syndrome (APS; onset or worsening of subpsychotic positive symptoms in the last twelve months), Brief Intermittent Psychosis Syndrome (BIPS; positive symptoms of psychotic intensity but below the threshold required for a DSM-IV Axis I psychotic disorder diagnosis), Genetic Risk and Deterioration (GRD; having a first-degree relative with a psychotic disorder and experiencing a deterioration of 30% or greater on the General Assessment of Functioning Scale in the past 12 months), or Schizotypal Personality Disorder (SPD; an Axis II personality disorder associated with development of psychosis (Kendler, Gruenberg, Strauss, 1981)). This subsample of the original 888 participants included 710 participants.

Longitudinal hypotheses were tested utilizing a subsample that included only subjects for whom data for substance use were available, who had baseline and 6-month follow-up symptom data for positive and negative dimensions of the Scale of Prodromal Symptoms (SOPS), and who met prodromal criteria as defined above. This subsample of the 710 participants utilized for the cross-sectional analyses included 297 participants.

Measures

Structured Clinical Interview DSM-III-R (SCID-I) Axis I Disorders, questionnaire and interview. (First et al., 1995). The SCID-I is a comprehensive assessment of the symptom criteria for DSM-III-R Axis I disorders (APA, 2004). This measure was used as a means of collecting data on substance used, as well as diagnosis of other Axis I disorders. For the present study, participants were classified into the following categories of AU: no alcohol use (no AU), alcohol use without impairment (AU), and alcohol abuse or dependence (AA/AD) and CU: no cannabis use (no CU), cannabis use without impairment (CU), and cannabis abuse or dependence (CA/CD).

Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al., 2002; Miller et al., 2002). The SIPS was used to assess prodromal symptomology. The Scale of Prodromal Symptoms (SOPS), a measure included in the SIPS, rates 19 symptoms along a six-point scale (ranging from healthy to pathological; 0 to 2: none, questionable, mild; 3 to 5: moderate, moderately severe, severe; 6: indicative of a potential psychotic state). Positive symptom scores between 3 and 5 are considered indicative of prodromal levels. The ratings were averaged to derive a score for each of five symptom dimensions. The symptom dimensions assessed include positive (Unusual Thought Content/Delusional Ideas, Suspiciousness/Persecutory Ideas, Gradiosity, Perceptual Abnormalities/Hallucinations, Disorganized Communication), negative (Social Anhedonia, Avolition, Expression of Emotion, Experience of Emotions and Self, Ideational Richness, Occupational Functioning), disorganized (Odd Behavior and

Appearance, Bizarre Thinking, Trouble With Focus and Attention, Personal Hygiene), and general (Sleep Disturbance, Dysphoric Mood, Motor Disturbance, Impaired Tolerance to Normal Stress). Previous research indicates that the measure is reliable (McGlashan et al., 2002) and predicts conversion to Axis I psychotic disorders (i.e., schizophrenia; Miller et al., 2002, 2003).

Results

Descriptive Statistics

The original sample included 888 participants. Participants without baseline positive symptom, negative symptom, alcohol use, or cannabis use data (n=178) were eliminated to yield 710 participants. A t-test was used to compare the mean age of the total sample to that of the sample used in the present study. The results indicated that participants from the original sample were significantly older than the subsample ($t(886)=2.84$, $p < 0.01$), indicating that older participants were less likely to have baseline symptoms ratings or information on substance use. A Chi^2 test was not significant when examining the difference between the proportion of males and females in the original sample and the subsample. There was a significant difference in the ethnic group distribution between the samples ($\chi^2(1, n=710) = 15.56$, $p = 0.02$) with more Asian participants (subsample = 6.8%, original = 2.8%) and fewer Multi-Racial participants in the subsample (subsample = 6.3%, original = 12.9%). There were significant differences between antidepressant medication use across groups ($\chi^2(1,N=888) = 25.23$, $p < 0.01$). The participants in the subsample were more likely than those in the original sample to

use antidepressant medication (subsample = 26.8%, original = 9.0%). A greater proportion of the subsample reported using antipsychotic medication than the original group ($\chi^2(1,N=888) = 5.92$, $p = 0.01$; subsample = 5.4%, original = 1.1%). Psychostimulant use did not differ between groups. The subsample reported more "other" psychotropic medication use than the original sample ($\chi^2(1,N=888) = 5.51$, $p = 0.02$; subsample = 7.7%; original = 2.8%). A greater proportion of the original sample reported completing college than the subsample ($\chi^2(1,N=871) = 30.23$, $p = 0.02$).

Comparisons of the BL symptom ratings of the total sample with the subsample indicated that there was a trend toward the original sample participants reporting more severe positive symptoms at baseline than the subsample ($t(76)=1.88$, $p = 0.06$; subsample mean = 1.65, SD = 1.18; original mean = 1.91, SD = 1.02). The samples did not differ on baseline negative symptom severity.

Of the 710 participants in the subsample, 413 had only baseline data (BL-only group) and 297 had both baseline and follow-up (FU group) data. T-tests were conducted to compare their demographic characteristics. The group with FU data reported more severe baseline negative ($t(687) = 10.22$, $p < 0.01$) and positive ($t(708) = 6.51$, $p < 0.01$) symptoms than the group with BL-only data. This indicates that participants with more severe symptoms at baseline were more likely to participate in FU interviews. The group with FU data was significantly older than the BL-only group ($t(596) = 3.04$, $p < 0.01$), indicating that older subjects are more likely to be retained for FU.

A Chi^2 test indicated that the proportion of males and females in the BL-only and FU sample did not differ ($\chi^2(1, N=710) = 0.15$, $p = 0.70$). There was, however, a significant difference in the ethnic group distribution between the samples ($\chi^2(6, N = 710) = 23.34$, $p < 0.01$). Differences were noted with more African American participants in the BL-only group (BL = 17.7%, FU = 7.1%) and fewer Caucasian participants in the BL-only group (BL = 65.6%, FU = 79.8%). There were significant differences between antidepressant medication use across groups ($\chi^2(1,N=710) = 19.24$, $p < 0.01$). A greater proportion of FU participants reported antidepressant medication use at baseline (BL = 20.6, FU = 35.4%). There was a trend for a greater proportion of antipsychotic use in the FU group than the BL-only group ($\chi^2(1,N=710) = 2.98$, $p = 0.06$; BL = 4.1%, FU = 7.1%). There was a significant difference between psychostimulant use between groups ($\chi^2(1,N=710) = 5.38$, $p = 0.02$) with more use in the BL-only group relative to the FU group (BL = 12.8%, FU = 7.4%). There was not a significant difference between groups on use of other psychotropic medications and no significant differences were found in highest levels of education completed.

As illustrated in Tables 1 and 2 the alcohol and cannabis use rates of the entire subsample (N=710) was comparable to the use rates of the baseline and follow-up subsample (N=297). The BL-only group did not differ from the FU group on rates of alcohol use ($\chi^2(2,710)=0.08$, $p = 0.96$) but did differ on rates of cannabis use ($\chi^2(2,710)=12.84$, $p < 0.01$). There was a higher proportion of participants in the BL-only group who do not use cannabis (BL = 73.1%, FU =

64.0%). The FU group reported more cannabis abuse/dependence than the BL-only group (BL = 10.2%, FU = 19.5%).

The BL-only subsample of participants examined in cross-sectional analyses include 40.6% females (N = 710; M age = 17.56, SD = 4.35). Approximately 71% of the sample identified as Caucasian (0.1% Native American, 6.8% Asian American, 0.1% Pacific Islander, 13.2% African American, 6.3% Multi-Racial, 1.8% Other). The majority (52%) of the sample reported taking a psychotropic medication (26% antidepressant, 5.4% antipsychotic, 10.4% psychostimulant, 7.3% other psychotropic medication, 2.5% missing data). The sample included a wide range of ages (10.6-45.3) and this likely influenced the varied reports of highest level of education completed (3.8% elementary school, 32.1% junior high, 31.6% some high school, 11.4% high school graduates, 19.7% some college or a college degree).

The FU subsample of participants examined in longitudinal analyses include 39.7% females (N = 297; M age = 18.15, SD = 4.58). Approximately 80% of the sample identified as Caucasian (5.1% Asian American, 7.1% African American, 6.1% Multi-Racial, 2.0% Other). The majority (61%) of the sample reported taking a psychotropic medication (35% antidepressant, 7.0% antipsychotic, 7.3% psychostimulant, 7.3% other psychotropic medication, 3.7% missing data). The sample included a wide range of ages (12-36.8) and this likely influenced the varied reports of highest level of education completed (2.7% elementary school, 28.6% junior high, 31.7% some high school, 13.1% high school graduates, 23.3% some college or a college degree).

Substance Use

Alcohol use disorders (AUDs) are often the most common comorbid disorders in schizophrenia (Brady, Casto, Lydiard, Malcolm, et al., 1991; Cantor-Graae, Nordstrom & McNeil, 2001; Drake & Mueser, 2002; Fowler, Carr, Carter & Lewin, 1998; Swofford, Kasckow, Scheller-Gilkey, & Inderbitzin, 1996). Approximately 28% to 47% of patients with schizophrenia or another psychotic disorder are dependent on or abuse alcohol (Addington & Addington, 2007; Cantor-Graae, Nordstrom & McNeil, 2001; Kavanagh, Waghorn, Jenner, Chant, Carr, Evans, et al., 2004; Mueser, Yarnold, Levinson, Singh, Bellack, Kee, et al., 1990). The baseline data sample and the follow-up data sample both consisted of 10.4% of participants reporting alcohol abuse/dependence. This indicates that our sample of putatively prodromal individuals and normal controls report less alcohol abuse/dependence than is typical of patients diagnosed with a psychotic disorder.

Previous research examining use rates of cannabis in participants diagnosed with a psychotic disorder indicate that abuse/dependence varies from 12%-43% (Bersani, Olandi, Kotzalidis, & Pancheri, 2002; Hambrecht & Hafner, 2000; Kumra, Thaden, DeThoma, & Kranzler, 2005; Margolese, Malchy, Negrete, Tempier, & Gill, 2004; Sevy, Robinson, Holloway, Alvir, Woerner, Bilder et al., 2001). Normal controls report 12-13% rate of cannabis abuse/dependence through 12th grade (Hambrecht & Hafner, 2000; Rey, Martin, & Krabman, 2004). Participants in the subsample with baseline data reported 14.1% cannabis abuse/dependence rate and 19.5% of the participants with follow-

up data reported cannabis abuse/dependence. These rates are higher than the cannabis abuse/dependence rates seen in the general population suggesting that our sample, which includes putatively prodromal individuals, is more likely to report cannabis abuse/dependence than normal adolescents.

Regression Analysis Results

In the regression analyses described below, AU and CU were coded in the following manner: no alcohol use = 0, alcohol use without impairment = 1, alcohol abuse/dependence = 2; no cannabis use = 0, cannabis use without impairment = 1, cannabis abuse/dependence = 2.

Cross-sectional Analyses of Baseline Symptoms

Baseline negative symptoms. As shown in Table 3, the results of the regression analysis of baseline negative symptom scores indicated significant main effects of CU and AU; however the addition of the interaction term resulted in a significant increase in the R^2, and a significant, independent interaction effect of CU and AU on ratings of negative symptoms.

To determine the nature of this interaction, negative symptom scores of cannabis nonusers, users, and those reporting abuse/dependence were compared within categories of AU with a Least Significant Difference (LSD) t-test. Among those who did not report alcohol use, participants who reported cannabis abuse/dependence showed higher negative symptom scores than those who do not use cannabis (LSD mean difference = 0.64, $p = 0.04$). Similar to participants who do not use alcohol, among participants who reported alcohol use without impairment there was a trend for those who reported cannabis abuse/dependence

to show higher negative symptom scores than those who do not use cannabis (LSD mean difference = 0.36, $p = 0.06$). In contrast, no significant differences in negative symptoms were noted between levels of cannabis use among participants who report alcohol abuse/dependence. The results remain significant after controlling for the significant demographic characteristics. As illustrated in Figure 1, the nature of the relation between CU and negative symptoms varies greatly as a function of AU. Also apparent in Figure 1 is the inverse main effect of AU on negative symptoms, such that subjects with no AU tend to show more pronounced negative symptoms.

It was hypothesized that the differences noted in negative symptom severity could be partially explained by one negative symptom in particular, baseline social functioning. Baseline social functioning was examined using a measure of social anhedonia. For this variable the participants were asked about their friendships, how comfortable they are with others, how much of their free time is spent socializing, and their level of interest in social activities. The results of the analyses of social anhedonia are shown in Table 4. When entered on the first block, there was a significant main effect of AU and CU, and a significant R^2. But the addition of the interaction term resulted in a significant increment in R^2, indicating the relation of AU with social anhedonia is moderated by CU.

To determine the nature of this interaction, social anhedonia scores of cannabis nonusers, users, and those reporting abuse/dependence were compared within categories of AU. Among those who did not report alcohol use or who used alcohol without impairment, no differences were noted in social anhedonia

levels as a function of cannabis use. Among participants who reported alcohol abuse/dependence, there was a trend for participants who reported cannabis use to show higher social anhedonia symptom scores than those who do not use cannabis (LSD mean difference = 1.16, $p = 0.08$). The results remain significant after controlling for the significant demographic characteristics. Figure 2 implies that there would be a significant inverse main effect of AU, such that those who do not use alcohol show the highest level of social anhedonia.

In summary, participants who do not use alcohol and those who use alcohol without impairment who also report cannabis abuse/dependence evidenced more severe negative symptoms than their counterparts who did not use cannabis. Participants who reported alcohol abuse/dependence and used cannabis evidenced a trend toward more severe social anhedonia symptoms than those who did not use cannabis. This indicates that cannabis use and cannabis abuse/dependence are associated with more severe negative symptoms and social anhedonia scores.

These results are partially consistent with the hypothesis that there is an inverse relationship between AU and negative symptom severity at baseline (hypothesis 1). An inverse relationship was also predicted between CU and baseline negative symptom severity (hypothesis 3), however there was no evidence of this. In fact, the relation of CU with both negative symptoms and social anhedonia tended to be positive. The significant interaction between AU and CU indicates that the predicted inverse relationship is only supported for AU when comparing those with no or low levels of AU. Thus, visual inspection of the

means suggests that participants who use alcohol without impairment report less severe overall negative symptoms and less severe social anhedonia symptoms in particular than participants who do not use alcohol.

Baseline positive symptoms. As shown in Table 5, the results of the regression analysis of baseline positive symptom ratings indicated significant main effects of CU and AU when entered on the first block, and the addition of the interaction term did not result in a significant increase in the R^2. The main effects of CU and AU were in the opposite direction, such that AU was associated with lower positive symptom ratings, whereas, consistent with predictions, CU was linked with higher positive symptom scores. The results remain significant after controlling for the significant demographic characteristics.

Mean comparisons among AU groups showed that no alcohol and alcohol abuse/dependence are associated with more severe positive symptoms when compared to alcohol use without impairment (no AU = $t(634) = 2.14$, $p = 0.03$; AA/AD = $t(137) = 3.08$, $p < 0.01$). Participants who reported alcohol abuse/dependence also endorsed more severe positive symptoms compared to participants who do not use alcohol ($t(473) = 1.67$, $p = 0.05$). These results do not depict a simple relationship between AU and baseline positive symptom severity and therefore are not consistent with the hypothesis that there will be a positive and dose-dependent relationship between AU and baseline positive symptom severity (hypothesis 2). Rather, it is more accurate to describe the relationship as U-shaped, with participants who use alcohol without impairment evidencing the

least severe positive symptoms compared to those who do not use and those who report abuse/dependence. See Figure 3.

As show in Figure 4, consistent with prediction, the direct relation between CU and positive symptom severity indicates that an increase in cannabis use is associated with an increase in positive symptom severity. There is a trend for less severe positive symptom ratings in those who do not use cannabis compared to those who use cannabis ($t(608) = 1.41$, $p = 0.08$). There is a significant difference in mean positive symptom severity in the participants who use cannabis without impairment when compared to those who report cannabis abuse/dependence ($t(216) = 2.12$, $p = 0.04$). These results are consistent with the hypothesis that there will be a positive, dose-dependent relationship between CU and positive symptom severity at baseline (hypothesis 4). The results remain significant after controlling for the significant demographic characteristics.

Longitudinal Analyses of Follow-up Symptoms

In order to test for the relation of CU and AU with symptom ratings at follow-up, controlling for baseline symptom severity, regression analyses were conducted with baseline symptom score entered on the first block, the main effects on the second block, and then the interaction term. The results for the analysis of negative symptoms at follow-up are presented in Table 6. The results show a significant increment in R^2 when the main effects are entered on block 2. However, neither CU nor AU showed a significant independent main effect in predicting follow-up negative symptoms, after controlling for baseline negative symptoms. Thus, CU and AU do not improve prediction of follow-up negative

symptom severity beyond that explained by baseline negative symptoms. These results are inconsistent with the hypothesis that there will be a positive relationship between AU and increased negative symptom severity at follow-up (hypothesis 5).

Similar results were obtained by the analysis of follow-up positive symptoms. The results in Table 7 show that positive symptom ratings at baseline are highly correlated with follow-up positive symptoms, providing strong support for the temporal stability of the ratings. But again, neither CU nor AU contributed to the prediction. These results are inconsistent with the hypothesis that there will be a positive relationship between CU and increased positive symptom severity at follow-up (hypothesis 6).

In order to test for the relation of CU and age with symptoms ratings at follow-up, controlling for baseline symptom severity, regression analyses were conducted with baseline symptom score entered on the first block, the main effects on the second block, and then the interaction term (age*CU). The results for the analysis of positive symptoms at follow-up are presented in Table 8. The results indicate that age did not show a significant independent main effect in predicting follow-up positive symptoms, after controlling for baseline positive symptoms. The interaction term was also nonsignficant. These results are inconsistent with the hypothesis that age is a significant moderator of the relation between CU and positive symptoms (hypothesis 7).

The results in Table 9 also show a main effect of CU, in that cannabis use is associated with more severe positive symptom ratings at baseline. Baseline age and the interaction term did not contribute to the prediction.

Discussion

As described above, alcohol and cannabis are the most commonly used and abused substances among psychiatric patients (Kavahagh, Waghorn, Jenner, Chant, Carr, Evans, et al., 2004). There is evidence that AU and CU are related to the course of illness and the symptom profile of persons with, and at risk for, schizophrenia and other psychotic disorders. Given the different chemical profiles of these substances, it is possible that they are associated with different symptom profiles and illness course. Further, recent research indicates that cannabis use may trigger or hasten the onset of psychotic disorders (Arendt & Munk-Jorgensen, 2004; Arseneault, Cannon, Witton & Muray, 2004; Degenhardt, Hall, & Lunskey, 2003; Zammit, Allebeck, Andreasson, Lundberg & Lewis, 2002).

To date, there has been little research on substance use or abuse in individuals at clinical risk for psychosis, particularly those who manifest prodromal signs. Further, there are no published reports on the independent and/or interactive effect of these substances. However, use of cannabis and other substances is positively correlated in general and clinical populations (Drake & Wallach, 1989; Butler, Jenkins, & Braff, 1993). The present study was designed to address this gap in the literature on AU and CU, and examine their main and interactive effects on prodromal symptom severity and the progression. This study

also afforded analysis of the association with varying levels of CU and AU. Persons with schizophrenia often evidence alcohol-related problems without meeting criteria for a disorder, that is, without alcohol abuse or dependence (Drake & Wallach, 1989; Drake, Osher, Noordsy, Hurlbut, Teague, & Beaudett, 1990; D'Souza, Abi-Saab, Madonick, Forselius-Bielen, Doersch, Braley, et al., 2005). The majority of published reports focus on patients with AUDs and CUDs, and relatively few address use in the absence of abuse or dependence. Further, the general trend in past research suggests that nearly half of schizophrenia patients who use alcohol or cannabis begin before the onset of the disease (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002; Cantor-Graae, Nordstrom & McNeil, 2001; Dixon, 1999), and substance use is more pronounced in the first year following onset of psychosis than in the subsequent two years (Addington & Addington, 2007). The present study adds to this body of literature by examining CU and AU in the prodrome, which may be a time of increased vulnerability.

Substance Use and Baseline Negative Symptoms

Extending previous findings, the present results indicate that *not* using alcohol or cannabis is associated with more severe negative symptoms in general, and more severe social anhedonia in particular than use without impairment. Thus, the participants who have fewer friends and spend more time alone are not using alcohol or cannabis and are reporting more severe negative symptoms. In contrast, participants who report lower levels of social anhedonia are more likely to use alcohol without impairment.

These findings are partially consistent with the first hypothesis that predicted an inverse relationship between AU and negative symptoms at baseline, and that better baseline social functioning will be associated with AU. The significant interaction between AU and CU indicates that the predicted inverse relationship is most pronounced for those with low levels of CU. This is consistent with previous research. Specifically, extant research indicates that participants with schizophrenia who endorse substance use evidence less severe negative symptoms than those who do not use substances (Talamo, Centorrino, Tondo, Dimitri, Henne, & Baldessarini, 2006). Dual-diagnosis participants (psychosis and SUD) manifest premorbid social functioning as good as or better than those who do not use substances (Larsen, Melle, Auestad, Friis, Haahr, Johannessen, et al., 2006; Swartz, Wagner, Swanson, Stroup, McEvoy, McGee, et al., 2006). Mirroring findings in nonclinical samples, alcohol experimentation and use with friends is normative and associated with typical adolescent development (Johnston, O'Malley, & Bachman, 1996; Engles, Knibbe, & Drop, 1999).

The findings are, however, only partially consistent with the first hypothesis, in that the inverse relationship was not maintained at the highest level of AU. Thus the relation of negative symptoms with AU was U-shaped. Specifically, participants who report no AU, or alcohol abuse/dependence, showed a higher level of negative symptoms relative to those who use alcohol without impairment. The explanation for the elevation in negative symptoms at the extremes of AU may differ.

Some past data are consistent with the finding that alcohol use at the level of abuse/dependence is associated with more severe negative symptoms. One group of researchers found that negative symptoms were more severe in participants with comorbid disorders (Cassano, Pini, Saettoni, Rucci, & Del'Osso, 1998). However, the comorbid disorders included in this research were not limited to AUDs; anxiety disorders, such as panic disorder, phobias, and obsessive-compulsive disorder, also evidenced more severe negative symptoms in participants with a psychotic disorder. In a review of 262 outpatient's charts who had at least 10 hospital visits within a 2-year period, researchers found that participants who reported obtaining treatment for their alcohol use also reported more negative symptoms than participants with past or current alcohol use that did not require treatment (Swofford, Scheller-Gilkey, Miller, Woolwine, & Mance, 2000). Another study found that participants with a dual-diagnosis of schizophrenia and alcohol abuse endorsed more severe negative symptoms than those with only schizophrenia (Bowie, Serper, Riggio, & Harvey, 2005).

A possible explanation for the finding that alcohol abuse/dependence is associated with more severe negative symptoms while alcohol use at a less severe level is not, is that participants who abuse alcohol may be less compliant with treatment regimens. Evidence from one report indicates that comorbid substance misuse was associated with poor medication compliance (Kamali, Kelly, Gervin, Browne, Larkin, & O'Callaghan, 2001). Another explanation is that the exacerbation of negative symptoms associated with alcohol abuse/dependence only occurs at this severe level of use. Research from healthy participants

indicates that alcohol abuse during late adolescence and early adulthood is associated with social impairments, increased risks of mood, anxiety, and personality disorders, and abuse of other substances in middle and late adulthood (Brown, McGue, Maggs, Schulenberg, Hingson, Swartzwelder, et al., 2008; Hasin, Stinson, Ogburn, & Grant, 2007).

An inverse relationship was also predicted between CU and baseline negative symptom severity (hypothesis 3), however there was no evidence of this. In fact, although there was no main effect of CU on negative symptoms or social anhedonia, the relation of CU with both negative symptoms and social anhedonia tended to be positive. Among participants who do not use alcohol or use alcohol without impairment, endorsement of cannabis use or cannabis abuse/dependence was associated with more severe negative symptoms and worse social functioning. In fact, the combination of no AU paired with cannabis abuse/dependence was associated with the most severe negative symptoms. These results highlight the importance of examining CU and AU in conjunction.

As is the case with AU, there are research findings that suggest that CU is associated with fewer negative symptoms and better premorbid adjustment in schizophrenia (Arndt, Tyrrell, Flaum, & Andreasen, 1992; Compton, Furman, & Kaslow, 2004; Dixon, Haas, Weiden, Sweeney, & Fances, 1990; 1991; Mueser, Yarnold, Rosenberg, Swett, Miles & Hill, 2000). These reports did not, however, examine CU as a function of AU. The findings of the present study indicate that CU is only linked with a reduction in negative symptoms when it is paired with

moderate AU. As shown in Figure 2, those who use cannabis with alcohol have lower negative symptoms than those who use neither cannabis nor alcohol.

Consistent with the findings presented here, there is some evidence to suggest that the better social functioning associated with alcohol use is unique to this substance. In one study, patients with schizophrenia and an AUD and those with schizophrenia only, were better socially adjusted than those with schizophrenia who used illegal substances such as cannabis (Modestin, Gladen, & Studer, 2001). Similarly, another group of researchers found that participants with schizophrenia who use alcohol had fewer negative symptoms than those who use other substances (Swofford, Scheller-Gilkev, Miller, Woolwine & Mance, 2000). As noted above, there are also experimental research findings that reveal an acute detrimental effect of cannabis use on negative symptoms in healthy participants (D'Souza, Perry, MacDougall, Ammerman, Cooper, Wu, et al., 2004; Sewell, Ranganathan, D'Souza, 2009).

Taken together, these findings suggest that AU is linked with social functioning in a manner that distinguishes it from other substances. Compared to CU, moderate AU may be more likely to occur within social contexts and/or to facilitate social motivation.

Substance Use and Baseline Positive Symptoms

There were main effects of AU and CU in the prediction of current prodromal positive symptom severity. The U-shaped relation between levels of alcohol use and positive symptom severity scores indicate that participants who reported alcohol use without impairment endorsed the least severe positive

symptoms, whereas participants who reported alcohol abuse/dependence had the most severe positive symptoms, followed by those who do not use alcohol.

These results are inconsistent with the predicted direct and dose-dependent relation between AU and baseline positive symptom severity stated in the second hypothesis. Rather, the results indicate that participants who use alcohol without impairment evidence less severe prodromal positive symptoms than those who do not use alcohol. These findings are also inconsistent with the evidence that in schizophrenia outpatients, the detrimental effects of AUDs on outcome measures including conceptual disorganization and rehospitalization, both of which are linked with positive symptom severity, occurred in a direct and dose-dependent pattern (Osher, Drake, Noordsy, Teague, et al., 1994). Other research on psychotic disorders also suggests a positive relation between alcohol and other substance abuse and more severe positive symptoms (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002; Duke, Pantelis, & Barnes, 1994; Fowler, Carr, Carter, & Lewin, 1998).

One explanation for these findings is that, in a manner similar to that seen with negative symptoms, participants who suffer from fewer positive symptoms may be more likely to have friends, and that these friendships, in turn, afford opportunities to use alcohol without impairment. Participants with more severe positive symptoms either do not use alcohol or report alcohol abuse/dependence. This pattern of relations may reflect differences in the causal direction of influence in the relation of AU with positive symptoms. Thus higher levels of positive symptoms may interfere with participation in the social contexts that

afford moderate AU. At the same time, excessive use at the level of alcohol abuse/dependence, may exacerbate positive symptoms severity. In other words, more severe positive symptoms may exert a prohibitive effect on social activities, thereby limiting alcohol use without impairment. This may also apply to negative symptoms, as no AU and severe AU are associated with more severe negative symptoms and worse social functioning.

It is also relevant to consider the present findings in light of past reports on the subjective effects of AU. There is some support, especially in the self-report literature, for the notion that some patients experience temporary relief from distress associated with positive symptoms and amelioration of dysphoria while consuming alcohol (Dixon, Haas, Weiden, Sweeney, & Frances, 1990; Eryshev, 2005; Gregg, Barrowclough & Haddock, 2007). This is consistent with a 'self-medication' hypothesis.

In contrast to AU, but consistent with prediction, the present study revealed a positive relation between CU and positive symptom severity in a dose-dependent fashion, such that those who abuse or are dependent on cannabis reported more severe positive symptoms than those who use cannabis without impairment. There was a trend for those who use cannabis without impairment to report more severe positive symptoms than those who do not use cannabis. The results presented here are consistent with the extant research on the relation between CU and positive symptom ratings (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002; Caspari, 1999).

Again, causality may go in either direction. As with AU, these may indicate exacerbation of positive symptoms by CU, or that more severe positive symptoms contribute to the likelihood of CU. The latter effect could be mediated by the goal of self-medication, or by a tendency for patients with more severe positive symptoms to be drawn to CU for some other reason.

As reviewed above, experimental research on the influence of cannabis on healthy participants indicates acute (minutes to several hours) induction of positive and negative symptoms (Bhattacharyya, Fusar-Poli, Borgwardt, Martin-Santos, Nosarti, O'Carroll, et al., 2009; D'Souza, Braley, Blaise, Vendetti, Olivery, Pittman, et al., 2008; D'Souza, Perry, MacDougall, Ammerman, Cooper, Wu, et al., 2004; Sewell, Ranganathan, D'Souza, 2009). It is possible that positive symptoms are exacerbated by CU in a dose-dependent fashion in participants with increased vulnerability for developing psychosis, and that these effects are more persistent than those seen in healthy participants. Similarly, substance use in prodromal participants may more dramatically and adversely affect already vulnerable neurotransmitter systems, thereby increasing symptom presentation in those with a predisposition to developing psychotic symptoms (Syed, Toshitaka, & Tomoji, 2004).

An alternative approach to interpreting the present findings is that a separate, third factor is associated with both heightened symptom severity and substance use. For example, unhealthy stress management techniques could account for both increased symptom severity and AU/CU; an individual may react to stressful life events by using substances, eating poorly, discontinuing

antidepressant medications, experiencing sleep disturbances, and withdrawing from social support systems, and these factors may increase both substance use and symptom severity.

Follow-up Symptom Severity

Baseline symptom severity was the best predictor of follow-up symptom severity for both negative and positive symptoms. Contrary to the fifth and sixth hypotheses, AU and CU did not improve prediction of follow-up symptoms. These results provide support for the temporal stability of prodromal symptom ratings and indicate that alcohol and cannabis use are not related to symptom progression in the time frame studied in this prodromal sample.

This is inconsistent with some of the findings in extant research on the relation between general substance use, cannabis use, and symptom progression. For example, researchers examining participants with schizophrenia found a positive association between a lifetime history of substance use and more severe symptoms at six-month follow-up (Kovasznay, Fleischer, Tanenberg-Karant, Jandorf, Miller, & Bromet, 1997). These researchers compared participants with schizophrenia spectrum disorders (schizophrenia, schizophreniform, and schizoaffective disorder) to participants with affective psychosis (bipolar or major depressive disorder with psychotic features). After adjusting for baseline scores on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), a lifetime history of a SUD and a schizophrenia spectrum disorder were associated with more severe BPRS ratings. This finding did not apply to SANS or SAPS ratings, and participants with a lifetime SUD and an affective psychosis disorder

did not show an association. Cannabis-specific findings also indicate a general trend in the literature for a positive association of CU with longitudinal exacerbation of psychotic symptom severity in patients with psychotic disorders (Arseneault, Cannon, Poulton, Murray, Caspi, & Moffitt, 2002; Degenhardt, Tennant, Gilmour, Schofield, Nash, Hall, et al., 2007; Miller, Johnstone, Lawrie, & Owens, 2006). Although these researchers found significant associations between CU and psychotic symptoms at follow-up, the association was weaker after controlling for baseline symptoms. This suggests that controlling for baseline symptom severity decreases the association and may be a contributing factor to some null-findings. That is, by controlling for baseline symptoms, the variance may be artificially constrained; in an attempt to clarify the relationship between substance use and follow-up symptom severity, an important and meaningful variable (baseline symptom severity) is removed. Thus, though the relationship is simplified by controlling for the potentially confounding variable, the relationship described may not accurately represent the association because an integral source of variation has been removed from the model (Meehl, 1971).

There are also findings that are consistent with those presented in this study. Researchers in one study retrospectively investigated the relation between SUDs and psychosis over an 18-month follow-up period in participants who recently experienced their first episode of psychosis (Lambert, Conus, Lubman, Wade, Yuen, Moritz, et al., 2005). Baseline SUD was not significantly associated with remission of psychosis. That is, the presence of psychotic symptoms at the follow-up was not associated with baseline SUD. Instead, remission of psychotic

symptoms was associated with the course of SUDs, such that those who decreased substance use were more likely to evidence remission than those with a more persistent SUD course. Another study examined 100 putatively-prodromal participants and cannabis use and dependence (Phillips, Curry, Yung, Adlard & McGorry, 2002). Cannabis use or dependence in the year prior to baseline was not associated with developing psychosis at the one-year follow-up. Premorbid symptoms were not taken into account in the analyses.

Additionally, one study suggests that current use is associated with more severe positive symptoms than a history of use in participants with dual-diagnoses (psychosis and a SUD; Margolese, Malchy, Negrete, Tempier, & Gill, 2004), suggesting that the association between more severe positive symptoms and SUDs is at least partially temporally linked. Further, research suggests that the relation between less severe negative symptom scores and alcohol use may be manifested only after chronic use (Buhler, Hambrecht, Loffler, an der Heiden & Hafner, 2002). Specifically, the findings indicate that significant results were noted in dual-diagnosis and single diagnosis psychosis participants only after five years.

Together these results suggest that substance use at baseline may not be a specific predictor of the progression of psychotic symptoms. Rather, the pattern of use (e.g., lifetime but not current use compared to more persistent use or acute compared to chronic use) may be more informative of the relationship between substances and psychotic symptoms. In addition, it may be necessary to follow participants for longer periods to fully elucidate the relation between substance use and symptom progression.

Finally, it is important to emphasize that the present study is focused on a prodromal sample, as opposed to patients diagnosed with psychosis, and that they are in a developmental period that tends to be characterized by significant behavioral change. This is important because, based on past reports, most youth (i.e., >50%) who meet current criteria for the prodrome do not go on to develop a psychotic disorder. Instead, these individuals tend to manifest a significant reduction in symptoms over time, as observed in the present study. Thus, the relation between substance use and symptom progression may be attenuated by the nature of the sample's clinical status and developmental stage.

Cannabis Use and Age

Inconsistent with the hypothesis that age would moderate the relation between CU and positive symptom severity at follow-up, there was no main or interactive effect of age in predicting follow-up positive symptoms, after controlling for baseline positive symptoms. In other words, the relation of CU with positive symptoms at follow-up was not moderated by age. This hypothesis was based on evidence from previous basic and clinical research that adolescents may be more susceptible to the deleterious effects of cannabis (Binder & Scharfman, 2004; Chao, Rajogopal, & Lee, 2006) and that earlier cannabis use (between ages 15 and 18 years) appears to confer increased risk of psychosis (Arseneault, Cannon, Poulton, Murray, Caspi & Moffit, 2002; Di Forti, Morrison, butt, & Murray, 2007; Jockers-Scherubl, Wolf, Radzei, Schlattmann, Rentzsch, Gomez-Carrillo de Castro, et al., 2007; Semple, McIntosh, & Lawrie, 2005; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002).

While the present findings do not indicate that the progression of positive prodromal symptoms is exacerbated by earlier CU, this does not preclude an interactive effect of age and CU on psychosis onset. Given that previous clinical studies reported an interaction of CU with age at onset of CU focused on psychosis onset as the dependent variable, the present study does not constitute an attempt at replication of the earlier findings.

Potential Mechanisms

Alcohol

The effects of alcohol and cannabis on the brain differ, and these differences may have implications for the nature of their relation with symptom severity and course. Research indicates that alcohol likely has deleterious effects on the developing brain by acting on the hippocampus and the prefrontal cortex. Findings from the present study indicate a U-shaped relationship of AU with negative and positive symptoms at baseline. AU without impairment is associated with the least severe negative and positive symptoms. In the case of negative symptoms, no AU is associated with the most severe presentation, whereas alcohol abuse/dependence is associated with the most severe positive symptoms.

It is possible that the direction of the causal relation between AU and symptoms differs at the extremes of the U-shaped curve. In other words, high levels of symptoms may impede social access to alcohol, whereas excessive alcohol abuse and dependence may contribute to symptoms.

For example, it may be that there are multiple pathways to the development of a psychotic disorder. Some individuals at risk for developing a

psychotic disorder may experience such severe negative symptoms that friendships and experimentation with alcohol may be untenable given their compromised social functioning, thus resulting in no AU. The findings presented in this study suggest that CU in these individuals is associated with the most severe negative symptoms. The predisposition toward psychosis may represent vulnerability in these individuals that results in an increased sensitivity to the detrimental effects of cannabis thus exacerbating their negative symptoms.

Other individuals at risk of developing a psychotic disorder may experience moderately severe negative symptoms that allow for the opportunity to form friendships and/or experiment with alcohol. However, these individuals may be more likely to develop alcohol abuse/dependence and use cannabis. Some research suggests that the dysregulation in dopamine and serotonin associated with a predisposition to develop a psychotic disorder may influence the neural substrates of reward (Hill, 2004) and result in increased risk of developing compulsive drug use (Koob, 1999). Thus, although these participants experienced mild enough negative symptoms to obtain alcohol and cannabis, they develop abuse/dependence, and the deleterious effects of these substances may result in exacerbation of symptoms. In this case, the findings may be another example of the heterogeneity of the development of psychosis.

The extant research on the relationship between AU and neural systems is primarily based upon cross-sectional experimental designs. Thus, although follow-up symptom analyses did not reveal a significant relationship with AU, it is possible that the hippocampus and prefrontal cortex may be susceptible to

alcohol-induced dysmaturation that was not evidenced during the relatively short follow-up period of this study. Further, chronic use is likely an important aspect of substance use such that the detrimental effects may not be manifested with acute use.

Dysmaturation of hippocampal and prefrontal cortex areas is often associated with corresponding cognitive deficits. Extension of the analyses to include cognitive functioning measures may shed light on the nature of the association between AU and symptom severity and progression in youth at risk for developing psychosis. Based on previous findings, one would predict that detriments in cognitive functioning, specifically executive functioning and memory tasks, would be associated with AU.

Cannabis

Findings suggest that there are similarities between the effects of schizophrenia and Δ^9 THC on neurotransmitter modulation, specifically dopamine regulation (Leweke, Giuffrida, Wurster, Emrich, Piomelli, 1999; Sundram & Castle, 2007; Dean, Sundram, Bradbury, Scarr, & Copolov, 2001; Zavitsanou, Garrick, & Huang, 2004). Dopamine dysregulation is associated with psychotic symptoms (Davis, Kahn, Ko, & Davidson, 1991; Lieberman, Perkins, Belger, Chakos, Jarskog, Boteva, et al., 2001) and there is evidence that Δ^9 THC causes dopamine release in the nucleus accumbens and the prefrontal cortex (Gardner & Lowinson, 1991; Tanda, Pontieri, & Chiara, 1997). Experimental studies have shown that Δ^9 THC inhibits the release of a number of neurotransmitters in addition to dopamine (Katona, Sperlagh, Magloczky, Santha, Kofalvi, Czirjak, et

al., 2000; Schlicker & Kathmann, 2001). The neurotransmitter imbalance created by this exogenous modulation may influence symptom presentation and progression.

At baseline, there was evidence of a dose-dependent relationship between CU and negative and positive symptom severity. The magnitude of the association of CU with negative symptom severity varied as a function of AU, with the strongest relation among those with no AU. Further, there was a positive association between positive symptom severity and CU. It is possible that sensitization, or the progressive influence of chemicals on neurotransmitter systems that results in increased sensitivity to the detrimental effects, partially accounts for this finding.

It has been proposed that exogenous cannabinoids, like Δ^9 THC, have a similar effect on the brain as excess dopamine. Dopamine is thought to be significantly associated with psychotic symptoms (dopamine agonists elicit symptoms and antipsychotics block dopamine receptors; Davis, Kahn, Ko, & Davidson, 1991; Lieberman, Perkins, Belger, Chakos, Jarskog, Boteva, et al., 2001). There is evidence to suggest that Δ^9 THC causes dopamine release in the nucleus accumbens and the prefrontal cortex (Gardner & Lowinson, 1991; Tanda, Pontieri, & Chiara, 1997). Thus, similar to the effect of dysregulation observed in schizophrenia, the dose-dependent relation evidenced in the present study could be understood as increasing levels of dysregulation of dopamine and other neurotransmitter systems. This dysregulation could affect multiple neural systems

and result in exacerbation of underlying vulnerabilities to the development of psychosis.

In individuals with psychosis, there is evidence of excessive pruning of dopaminergic neurons that may lead to hypofrontality, likely as a result of interactions between the developing prefrontal cortex and multiple neurotransmitter systems (Retaux, Besson, and Penit-Soria, 1991; Benes, Taylor, and Cunningham, 2000). Hypofrontality, in turn, may lead to a reduction in mesocortical feedback and, therefore, a reduction in inhibition of the mesolimbic system (Milin, 2008). The mesocorticolimbic pathway is believed to play a role in the effects of stress (Kalivas & Stewart, 1991) and the onset of mental disorders is often associated with a precipitating stressful event (Norman & Malla, 1993). Exposure to Δ^9 THC may trigger or potentiate psychotic symptoms via its effects on HPA activity and increases in cortisol secretion (D'Souza et al., 2004). Thus, vulnerability and stress interact and it is possible that the neurotransmitter dysregulation associated with CU may mimic the neurodevelopmental process that precedes psychosis and result in more severe positive symptoms than would be evidenced without CU.

Limitations and Future Directions

Several limitations of the present study should be noted. First, the study is focused on a 6-month time frame. Some research indicates, however, that following participants for up to five years may be necessary to describe the full extent of the association between use and symptom severity. Second, the naturalistic, uncontrolled design of this study limits the questions about causality

that can be addressed. Third, there were significant differences between the baseline-only group and the participants with follow-up data. This could be indicative of a sample that is not representative of the population. Fourth, the substance use analyses were limited to alcohol use and cannabis use. Although these are the two most commonly used and abused substances, other illicit substances as well as nicotine, may also exert an affect that is not being addressed in the present study. In addition, although including measures of "no use," "use without impairment," and "abuse/dependence" represents an improvement over dichotomous "use/no use" this still represents forced categorization. That is, the use data were ordinal rather than continuous. This precluded the use of some analyses (e.g., curvilinear) that may have better explained the results. Finally, it is possible that self-report of substance use compromised the validity of the data. Nonetheless, there are findings indicating that self-report data on substance use is typically valid and that the use of urine or blood drug screens compromises external validity by reducing participation in research (Weaver, Madden, Charles, Stimson, Renton, Tyrer, et al., 2003; Weiss, Najavits, Greenfield, Soto, Shaw & Wynerm, 1998).

The participants who contributed follow-up data were more likely to be older, Caucasian, and use antidepressant medication than those with only baseline data. These participants also report more severe positive and negative symptoms and cannabis abuse/dependence. One may logically expect that older participants would be more likely to endorse misuse of cannabis as they have likely been afforded greater opportunities for exposure to and procurement of cannabis. The

highest risk period for psychosis is in the early 20s. Therefore, it is possible that the older participants who were included in the follow-up data were more distressed about their symptoms and thus were more likely to seek help through participation in the research protocol. Concomitantly, the majority of participants improve over time without intervention. Thus, younger, healthier persons may perceive fewer benefits from participating in a study of mental health than older participants who are both reporting more symptoms and are nearer to the high-risk age range. Together, these factors may have contributed to the age difference between the baseline-only and follow-up groups. This may be considered a limitation of this study; however, it would likely influence all studies of this type and therefore not exert undue influence on the results presented here relative to previous findings.

There were also differences in the rates of alcohol use in our sample compared to samples with a psychotic disorder. That our sample of putatively prodromal individuals and normal controls report less alcohol abuse/dependence than is typical of patients diagnosed with a psychotic disorder is likely a function of the younger age of our sample relative to most samples. It may also be that participants who have experienced a psychotic break, in addition to being older, are also more prone to self-medication than younger participants.

These limitations suggest several aspects that future research should incorporate into research designs. First, substance use data should be gathered in as comprehensive a manner as possible. Specifically, lifetime use and current use should be measured. Second, participants should be followed for a minimum five

years as there is at least one longitudinal study that found only trend level data until the fifth year of follow-up. Third, although experimental designs in this area would be unethical, thorough collection of relevant substance use data (lifetime versus current) in concert with a prospective design should be the standard rather than a rarity. This will allow for a better understanding of the temporal relationship between use and symptom profile. For example, lifetime but not current users could be compared to those who use at one time but not another. This would allow for analysis of symptoms before and after use and analysis of current use (within the past year) compared to past use (used for one year but has not use for the past three years).

Summary and Conclusions

The present study represented a significant improvement over most past studies in that it afforded the opportunity to examine the both the independent and interactive relations of AU and CU with prodromal symptoms. In many respects, the relations of CU and AU with prodromal symptoms parallels the relations observed between substance use and symptoms in psychotic disorders. Not using alcohol or cannabis is associated with more severe negative symptoms in general, and more severe social anhedonia in particular. Also consistent with previous findings, AU without impairment was associated with the least severe negative symptoms and increased levels of CU were associated with more severe negative and positive symptoms. It appears that substance use patterns are both a consequence and a precipitant of symptom severity and profiles.

The association of AU and CU with prodromal symptoms differs from extant findings in psychotic populations. Negative symptom severity at baseline is best described by considering the interactive association of AU and CU; previous research has not examined AU and CU's independent and interactive relation to symptom severity. Although previous research has generally revealed an association between AU and CU and psychotic symptom progression, this result was not found in the present study. This may be a consequence of the focus on prodromal, rather than psychotic symptoms, as well as the developmental stage of the present subjects with the follow-up window of 6 months. Future studies with longer term follow up assessments may reveal effects that were not detected during this time frame.

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Tables and Figures

Table 1.

Alcohol and Cannabis Use of Subsample (N=710)

	No Alcohol Use	Alcohol Use	Alcohol Abuse/Depend	Total
No Cannabis Use	377 (76.6%)	107 (21.7%)	8 (1.6%)	492 (69.3%)
Cannabis Use	11 (9.3%)	93 (78.8%)	14 (11.9%)	118 (16.6%)
Cannabis Abuse /Dependence	13 (13%)	35 (35%)	52 (52%)	100 (14.1%)
Total	401 (56.5%)	235 (33.1%)	74 (10.4%)	

Table 2.

Alcohol Use and Cannabis Use of Participants with Follow-Up Data (N=297)

	No Alcohol Use	Alcohol Use	Alcohol Abuse/Depend	Total
No Cannabis Use	150 (78.9%)	37 (19.4%)	3 (1.6%)	190 (64%)
Cannabis Use	7 (14.3%)	38 (77.6%)	4 (8.2%)	49 (16.5%)
Cannabis Abuse /Dependence	9 (15.5%)	25 (42.4%)	24 (41.4%)	58 (19.5%)
Total	166 (55.9%)	100 (33.7%)	37 (10.4%)	

Table 3

Results of Regression Analysis of Baseline Negative Symptom Ratings

	Predictors	Standardized Beta	T-value	R^2/R^2 change	F-value (df)
Block 1	AU	-0.22	-4.40**	0.03	9.67 (2,707)**
	CU	0.15	2.97*		
Block 2	AU	-0.29	-4.94**	0.03/0.007	5.29 (1,706)*
	CU	0.02	0.31		
	Interaction	0.20	2.30*		

Note. *p < 0.05, **p < 0.001

Table 4

Results of Regression Analysis of Baseline Social Anhedonia Symptom Ratings

	Predictors	Standardized Beta	T-value	R^2/R^2 change	F-value (df)
Block 1	AU	-0.23	-4.67**	0.04	14.45 (2,707)**
	CU	0.05	5.10*		
Block 2	AU	-0.33	-5.65**	0.05/0.01	9.83 (1,706)*
	CU	-0.12	-1.62		
	Interaction	0.27	3.14*		

Note. *p < 0.05, **p < 0.001

Table 5

Results of Regression Analysis of Baseline Positive Symptom Ratings

	Predictors	Standardized Beta	T-value	R^2/R^2 change	F-value (df)
Block 1	AU	-0.16	-3.19**	0.04	13.03 (2,707)**
	CU	0.25	5.10**		
Block 2	AU	-0.17	-2.86*	0.04/0.00	0.16 (1,706)
	CU	0.23	3.14*		
	Interaction	0.04	0.41		

Note. *p < 0.05, **p < 0.001

Table 6

Results of Regression Analysis of Follow-Up Negative Symptom Ratings

	Predictors	Standardized Beta	T-value	R^2/R^2 change	F-value (df)
Block 1	BLN	0.60	12.86	0.36	165.41 (1,295)**
Block 2	BLN	0.60	12.72**	0.37/0.01	3.22 (2,293)*
	AU	-0.03	-0.48		
	CU	-0.10	1.57		
Block 3	BLN	0.60	12.64**	0.37/0.00	0.03 (1,292)*
	AU	-0.04	-0.48		
	CU	-0.11	-1.18		
	Interaction	0.02	0.16		

BLN = Baseline Negative Symptom Ratings

Note. *p < 0.05, **p < 0.001

Table 7

Results of Regression Analysis of Follow-Up Positive Symptom Ratings

	Predictors	Standardized Beta	T-value	R^2/R^2 change	F-value (df)
Block 1	BLP	0.50	10.00**	0.25	100.10(1,295)**
Block 2	BLP	0.51	9.90**	0.26/0.00	0.46 (2,293)
	AU	0.06	0.95		
	CU	-0.03	-0.51		
Block 3	BLP	0.51	9.90**	0.26/0.00	2.50 (1,292)
	AU	-0.01	-0.10		
	CU	-0.15	-1.50		
	Interaction	0.19	1.58		

BLP = Baseline Positive Symptom Ratings

Note. *p < 0.05, **p < 0.001

Table 8

Results of Regression Analysis of Follow-Up Positive Symptom Ratings and Age

	Predictors	Standardized Beta	T-value	R^2/R^2 change	F-value (df)
Block 1	BLP	0.50	10.00**	0.25	100.10(1,295)**
Block 2	BLP	0.50	9.89**	0.26/0.00	0.69(2,293)
	Age	0.06	1.15		
	CU	-0.01	-0.18		
Block 3	BLP	0.50	9.89**	0.26/0.01	1.88 (1,292)
	Age	0.11	1.72		
	CU	0.28	1.29		
	Interaction	-0.31	-1.37		

BLP = Baseline Positive Symptom Ratings

Note. *p < 0.05, **p < 0.001

Figure 1.

Mean Baseline Negative Symptom Ratings across Levels of Alcohol and Cannabis Use

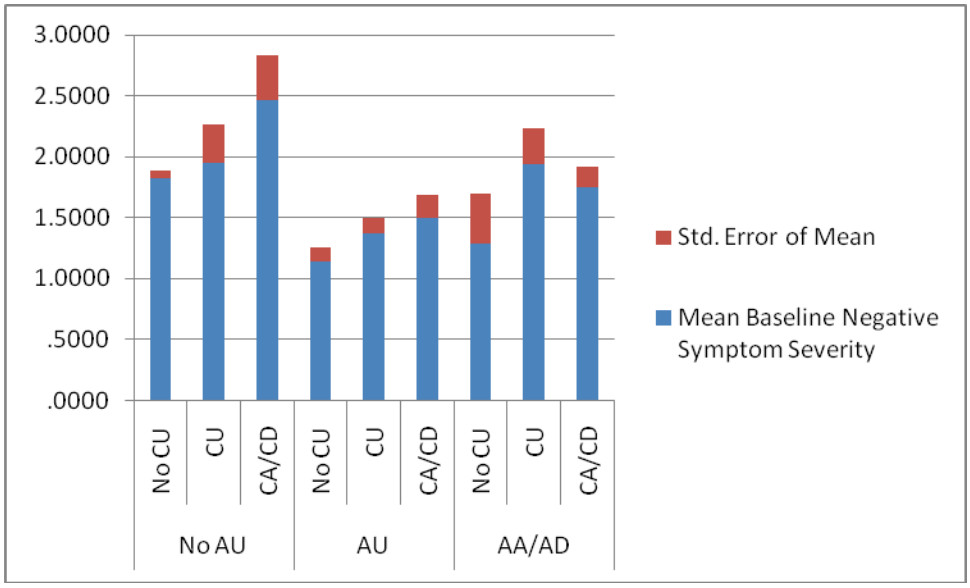

Figure 2.

Mean Baseline Social Anhedonia Symptom Ratings across Levels of Alcohol and Cannabis Use

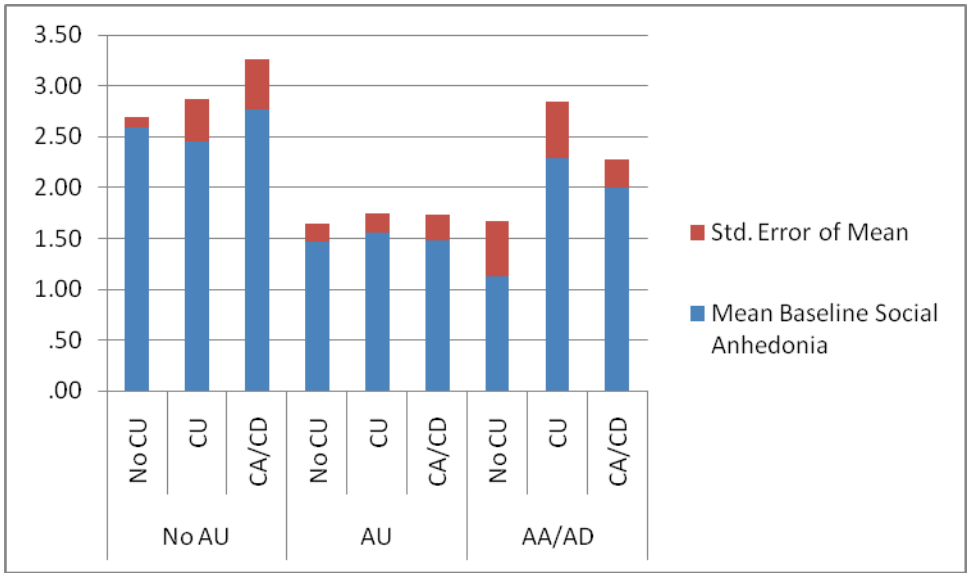

Figure 3.

Mean Baseline Positive Symptom Ratings across Levels of Alcohol Use

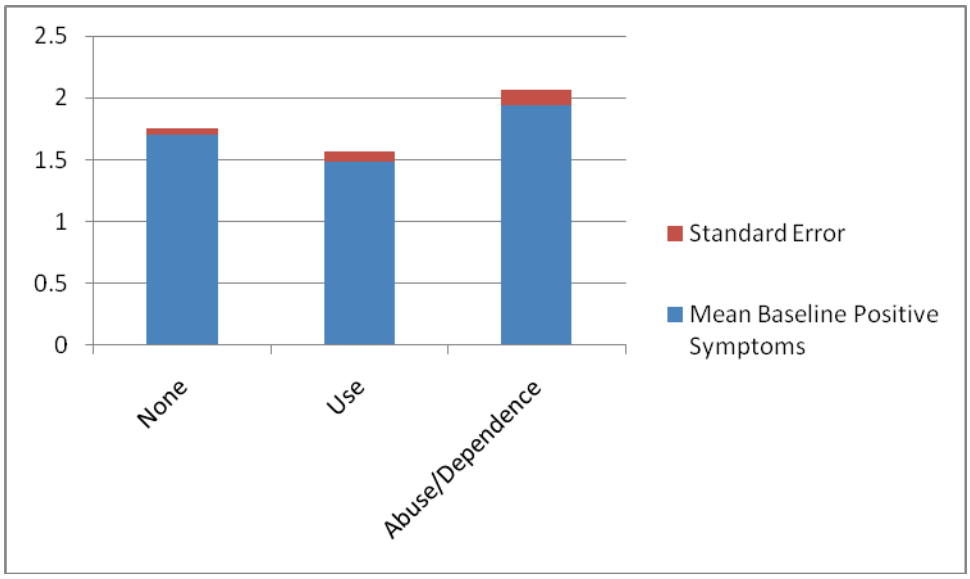

Figure 4.

Mean Baseline Positive Symptom Ratings across Levels of Cannabis Use