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## Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis

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### Abstract

Elevated rates of substance use (alcohol, tobacco, cannabis) have been reported in people at clinical high risk (CHR) of developing psychosis and there is some evidence that substance use may be higher in those who convert to a psychosis compared to non-converters. However little is known about the predictive value of substance use on risk of conversion to psychosis in those at CHR of psychosis. In the current study, 170 people at CHR of psychosis were assessed at baseline on severity of alcohol, tobacco and cannabis using the Alcohol and Drug Use Scale. Participants were recruited across three sites over a four year period as part of the Enhancing the Prospective Prediction of Psychosis (PREDICT) study. Predictors of conversion to psychosis were examined using Cox proportional hazards models. Results revealed that low use of alcohol, but neither cannabis use nor tobacco use at baseline contributed to the prediction of psychosis in the CHR sample. Prediction algorithms incorporating combinations of additional baseline variables known to be associated with psychotic conversion may result in increased predictive power compared with substance use alone.

### Keywords

alcohol; cannabis; prodrome; psychosis; substance use; tobacco

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### Conflict of Interest

All authors declare no conflict of interest.

### Contributors

The first author wrote the first version of the manuscript and performed data analysis. The second and third authors assisted in data collection, and provided laboratory space and funding. The fourth author assisted in data organization and data analysis. The fifth author assisted in data collection, provided laboratory space and funding, and assisted in the writing of the final version of the manuscript.

## 1. Introduction

In a recent review, Addington and colleagues (Addington et al., in press) identified ten studies that examined substance use in people who are at clinical high risk (CHR) of developing psychosis. Across these studies, the most commonly used substances were cannabis, alcohol and tobacco, with cannabis and tobacco use being higher than in healthy controls (Auther et al., 2012), and with rates similar to those experiencing a first-episode of psychosis (Barnett et al., 2007; Cooper et al., 2012; Sevy et al., 2001). Fewer studies have examined the relationship between substance use and conversion to psychosis in CHR. Cannon et al (Cannon et al., 2008) reported that a history of any substance abuse was one of five predictors of conversion to psychosis in a multivariate model. Kristensen and Cadenhead (Kristensen and Cadenhead, 2007) found that CHR individuals were more likely to develop psychosis within one year if they had used tobacco or met criteria for cannabis abuse/dependence. Several of the remaining studies examining substance use in those at CHR have reported no significant relationships between severity of use and later conversion to psychosis (Auther et al., 2012; Phillips et al., 2002; Ruhrmann et al., 2010; Thompson et al., 2011). However, some studies evaluated cannabis only (Korver et al., 2010), or recorded the use of any substance globally rather than multiple individual ones (Cannon et al., 2008; Thompson et al., 2011). In addition, it may be important to consider the role of positive symptoms as there is some evidence that cannabis use may be related to positive symptom severity (Corcoran et al., 2008; Korver et al., 2010). Furthermore, the negative studies may be underpowered to demonstrate a positive relation between substance use and conversion, or employed statistical tests insensitive to the predictive value of substance use for psychosis onset. As such, it is unclear whether there is an effect of substance use on conversion to psychosis in CHR individuals.

Therefore, the aim of the current prospective study was to examine in a large, well characterized sample of individuals at CHR of psychosis 1) severity of substance use at baseline in people who converted to a psychosis compared to non-converters over a four year period, and 2) the relationship between substance use at baseline and rate of conversion to psychosis.

## 2. Materials and Methods

### 2.1 Sample

One-hundred and seventy (96 males, 74 females) individuals at CHR of psychosis participated as part of a multi-site NIMH funded study “Enhancing the Prospective Prediction of Psychosis” (PREDICT). This was a 4-year longitudinal observational study to determine predictors of conversion to psychosis in individuals at CHR of developing psychosis who were not using anti-psychotic medication. The study was conducted at the Universities of Toronto, North Carolina, and Yale. All CHR individuals met the Criteria of Prodromal States (COPS) based on the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2010). One hundred sixty-seven CHR participants met attenuated positive symptom syndrome (APSS) criteria, which includes the emergence or worsening of a non-psychotic level disturbance in thought content, thought process or perceptual abnormality over the past year, six participants met criteria for genetic risk and deterioration

(GRD), which required either a first degree relative with a psychotic disorder or the subject having schizotypal personality disorder plus at least a 30% drop in functioning on the General Assessment of Functioning (GAF) scale in the past 12 months, and three participants met both APSS and GRD.

Participants were excluded if they met criteria for any current or lifetime axis I psychotic disorder, prior history of treatment with an antipsychotic, IQ<70, or past or current history of a clinically significant central nervous system disorder that may confound or contribute to clinical high risk symptoms, or using antipsychotics at baseline. Antipsychotics were not used at any later points in this study.

## 2.2 Measures

Criteria for a prodromal syndrome and for conversion to psychosis were determined using the SIPS (McGlashan et al., 2010). Conversion meant that at least one of the five attenuated positive symptoms reached a psychotic level of intensity (rated 6) for a frequency of 1 hour/day for 4 days/week during the past month or that symptoms seriously impacted functioning (e.g. severely disorganized or dangerous to self or others). Symptoms were assessed with the Scale of Prodromal Symptoms (SOPS), which consists of 19 items in 4 symptom domains: positive, negative, general, and disorganized.

Participants were rated on substance use with a well-established rating scale, the Alcohol and Drug Use Scale (AUS/DUS) (Drake et al., 1996). The AUS/DUS was used to record severity of substance use within the past month. It is a 5-point scale with anchors that are equivalent to 1=abstinent, 2=use without impairment, 3=abuse, 4=dependence and 5=severe dependence. Ratings of 3 and 4 reflect behaviors equivalent to DSM-IV diagnoses of abuse and dependence. Severity ratings were recorded for alcohol, tobacco, cannabis, cocaine, opiates, PCP, amphetamine, MDMA, GHB, huffing, hallucinogens and other substances at baseline.

## 2.3 Statistical Analysis

Differences in baseline characteristics of converters vs non-converters were evaluated by either *t*-tests (continuous data), or  $\chi^2$  or Fisher's Exact tests (categorical data). Pearson's rho was used to correlate substance use with age and symptom severity. Substance use variables were non-normally distributed and non-transformable; therefore, Mann Whitney U tests were used to compare substance use severity at baseline between groups. Cox proportional hazard regression models were used to estimate the association of substance use with conversion to psychosis. The assumption of proportionality was violated for ratings of tobacco use; therefore, ratings of 2–4 were combined as any use. The analysis of time to conversion was calculated in days since entry into the study. Follow-up for non-converters was calculated as the last date when SOPS ratings were acquired within 4 years. The effects of risk factors are described by their Cox regression hazard ratio (HR) and 95% confidence intervals. We first considered a model which included all the predictors that had a p-value <0.25 in the univariate analyses, with an aim to drop the least significant variable, then continue by successively refitting the model and applying the same backward elimination

rule until all remaining variables were statistically significant. Statistical analyses were conducted using SPSS 20.0 and SAS 3.0.

## 2.4 Procedures

All three sites involved in this longitudinal study of predictors of conversion to psychosis recruited CHR individuals. Raters were experienced research clinicians who demonstrated adequate reliability at routine reliability checks. Gold standard post-training agreement on the critical threshold for determining initial eligibility and subsequent conversion status based on the SIPS was excellent ( $\kappa=.90$ ). The PI or clinical psychiatrist or psychologist at each site conducted a comprehensive clinical assessment to determine if entry criteria were met. JA chaired weekly conference calls to review criteria for all individuals admitted to the study. The study protocols and informed consents were reviewed and approved by the ethical review boards of all three study sites. AUS/DUS ratings were acquired at the baseline assessment.

## 3. Results

### 3.1 Demographics

The mean age of the sample was 19.7 years ( $SD=4.5$ ). Demographic characteristics are shown in Table 1. Converters and non-converters did not significantly differ on age,  $t=0.19$ ,  $p=0.90$ , gender,  $\chi^2=1.08$ ,  $p=0.30$ , race,  $p=0.32$ , marital status,  $p=0.47$ , or education,  $p=0.41$ .

The use of substances other than alcohol, tobacco or cannabis was either minimal or absent, therefore the use of these substances were not considered further in relation to demographic variables, positive symptoms, or rate of conversion to psychosis. Age was significantly associated with use of tobacco,  $r=0.24$ ,  $p<0.01$ , and alcohol,  $r=0.42$ ,  $p<0.01$ , but not cannabis  $r=0.02$ ,  $p=0.76$ . Males and females did not differ on tobacco,  $p=0.79$ , alcohol,  $p=0.68$  or cannabis use,  $p=0.79$ . Total SOPS positive symptom scores did not significantly correlate with tobacco,  $r=0.04$ ,  $p=0.63$ , alcohol,  $r=-0.10$ ,  $p=0.22$ , or cannabis use,  $r=0.04$ ,  $p=0.59$ .

### 3.2 Substance use and risk of conversion to psychosis

Table 2 displays the number of participants receiving each of the ratings for the different substance.

When examining AUS/DUS severity ratings, converters and non-converters significantly differed in baseline alcohol use,  $U=1472.5$ ,  $p<0.01$ , reflecting slightly lower use severity in converters. Groups did not differ in tobacco,  $U=1752.5$ ,  $P=0.13$ , or cannabis use,  $U=1790.0$ ,  $P=0.19$ .

The predictors of conversion to psychosis examined via Cox regression were: Baseline alcohol, tobacco and cannabis use, and age. In the final model, reduced use of alcohol was the only significant predictor of risk of conversion to psychosis,  $p<0.05$ . Compared to those who used alcohol, those who did not use alcohol had 2.1% higher rate of conversion to psychosis per unit time,  $HR=2.1$ ,  $CI=1.02-4.28$ ,  $p<0.05$ . There was no association between tobacco or cannabis use at baseline and risk of conversion to psychosis.

## 4. Discussion

This multi-site study assessed prospectively the relationship between substance use at entry into a CHR for psychosis research program and rate of conversion to psychosis. Total SOPS positive symptoms did not significantly associate with use of alcohol, tobacco or cannabis. Slightly but significantly lower alcohol use was observed in those who converted to psychosis compared to non-converters. Low levels of alcohol use were associated with an increased rate of conversion to psychosis. Neither tobacco nor cannabis use severity predicted later conversion to psychosis; suggesting use of these substances did not contribute to the rate of conversion to a psychotic disorder in this sample.

These results should be interpreted with caution. Tobacco, cannabis and alcohol use did not increase the rate of conversion to psychosis, although it is possible that high endorsement of abstinence and unimpaired substance use, and commensurately minimal prevalence of abuse in the sample may limit sensitivity to detect an effect. The negative result between increased substance use and rate of conversion to psychosis accords with conclusions of a recent review of the literature (Addington et al., in press) on substance use in CHR, and suggests that substance use may not contribute uniquely to the prediction of psychosis in people at CHR of psychosis. Alcohol use with no impairment was limited in this sample of converters and may be a proxy measure of being more sociable. It is noteworthy that the current sample was larger and therefore greater powered than Kristensen and Cadenhead's (Kristensen and Cadenhead, 2007) sample of 48 CHR subjects, who demonstrated a relation between cannabis abuse and later conversion to psychosis at 1 year, which could suggest a sensitivity of the substance use effect to sample size.

It is important to note that the current prospective study lacks information on substance use diagnoses in people at CHR of psychosis. In addition, substance use was not measured longitudinally, and therefore the results cannot address potential changes in substance use over time in this population. Interestingly, Cannon and colleagues (Cannon et al., 2008) observed evidence for a relation between increased rate of conversion to psychosis and any substance use when entered in a prediction algorithm along with four additional predictors including psychopathology and social functioning. In this regard, it may be that the importance of substance use could be through its interactive effects with other substances, symptom severity or current level of functioning. The role of substance use for risk of conversion may be better tapped by multivariate prediction algorithms incorporating multiple variables implicated in psychosis onset, such as early trauma (Bechdolf et al., 2010), genetic risk (Cannon et al., 2008) or social functional impairment (Gee and Cannon, 2011), and may be informative in future research.

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**Table 1**

Demographic characteristics of the sample

	Non-converters (n=141)		Converters (n=29)	
	Mean (SD)	Range	Mean (SD)	Range
Age	19.8 (4.5)	12.0–31.0	19.7 (4.6)	12.3–31.2
	N	%	N	%
Gender (M:F)	82:59	59:41	14:15	48:52
Race				
Caucasian	113	79.6	19	65.5
Black/African American	13	9.2	5	17.2
Asian	9	6.3	3	10.3
Native Hawaiian/Pacific Islander	1	0.7	0	0
Other	5	3.5	2	6.9
Marital status				
Common law/Legal married	6	4.2	2	6.9
Separated	2	1.4	0	0
Never Married	134	94.4	27	93.1
Education				
Did not complete high school	61	43.0	13	44.8
GED/High school diploma	14	0.7	1	3.4
Some college, did not graduate	52	9.9	3	10.3
Community college/technical degree	5	36.6	7	24.1
College graduate	4	3.5	2	6.9
College graduate and some Master's level courses	3	2.8	2	6.9
Master's degree completed	2	2.1	1	3.4

**Table 2**

Rates of drug use as reported in the AUS/DUS interview at baseline<sup>1</sup>.

Baseline AUS/DUS assessment	Non-converters (n=141)		Converters (n=29)	
	N	%	N	%
<b>Alcohol</b>				
Abstinent	56	39.7	20	68.9
Use without impairment	81	57.5	8	27.6
Abuse	3	2.1	0	0.0
Dependence	1	0.7	1	3.4
<b>Tobacco</b>				
Abstinent	94	67.1	24	82.8
Use without impairment	43	30.5	3	10.4
Abuse	2	1.4	1	3.4
Dependence	2	1.4	1	3.4
<b>Cannabis</b>				
Abstinent	95	67.4	23	79.3
Use without impairment	33	23.4	5	17.3
Abuse	11	7.8	0	0.0
Dependence	2	1.4	1	3.4
<b>Cocaine</b>				
Abstinent	131	92.3	28	96.6
Use without impairment	9	6.3	1	3.4
Abuse	0	0.0	0	0.0
Dependence	1	0.7	0	0.0
<b>Opiates</b>				
Abstinent	139	97.9	29	100.0
Use without impairment	0	0.0	0	0.0
Abuse	1	0.7	0	0.0
Dependence	1	0.7	0	0.0
<b>PCP</b>				
Abstinent	141	100.0	29	100.0
<b>Amphetamines</b>				
Abstinent	138	97.9	29	100.0
Use without impairment	3	2.1	0	0.0
<b>MDMA</b>				
Abstinent	135	95.7	28	96.6
Use without impairment	6	4.3	1	3.4



Baseline AUS/DUS assessment	Non-converters (n=141)		Converters (n=29)	
	N	%	N	%
<b>GHB<sup>2</sup></b>				
Abstinent	139	98.6	29	100.0
Use without impairment	1	0.7	0	0.0
<b>Huffing</b>				
Abstinent	140	99.3	29	100.0
Use without impairment	1	0.7	0	0.0
<b>Hallucinogens</b>				
Abstinent	128	90.8	28	96.6
Use without impairment	11	7.8	1	3.4
Abuse	2	1.4	0	0.0
<b>Other Substances</b>				
Abstinent	135	95.7	29	100.0
Use without impairment	6	4.3	0	0.0

<sup>1</sup> Only ratings that were endorsed have been included in this table.

<sup>2</sup> Data was missing for one participant in the non-converter group.