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Negative Symptoms are Associated with Less Alcohol Use, Craving, and "High" in Alcohol Dependent Patients with Schizophrenia

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Abstract

Background—Alcohol use disorders (AUDs) frequently co-occur with and exacerbate schizophrenia, yet the specific relationships between schizophrenia symptoms and alcohol use remain unclear.

Methods—PANSS scores were correlated with measures of alcohol and other substance use in patients with schizophrenia-spectrum disorders and AUDs entering a trial of monitored naltrexone treatment. Data were analyzed from the first 80 participants; 55% had schizophrenia and 45% had schizoaffective disorder. All had AUDs; 95% had alcohol dependence and 5% alcohol abuse; 34% also had cannabis abuse/dependence and 31% cocaine abuse/dependence.

Results—PANSS Negative scores were inversely correlated with Addiction Severity Index alcohol composite score, alcohol craving, quality of alcohol "high" (euphoria), and with frequency of cannabis use. An exploratory analysis indicated that the negative symptoms that may most strongly correlate with less alcohol use, craving or euphoria were passive/apathetic social withdrawal, blunted affect, difficulty in abstract thinking, and stereotyped thinking. Higher PANSS Composite scores, indicating the predominance of positive over negative PANSS symptoms, correlated with more alcohol craving and cannabis use. Higher PANSS General scores were associated with more alcohol craving.

Conclusions—These findings extend previous reports of the association of negative schizophrenia symptoms with less alcohol and substance use to patients with AUDs and indicate that this

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relationship also includes less alcohol craving and less alcohol euphoria. The findings may also provide some initial evidence that specific negative symptoms may be key to these relationships.

Keywords

schizophrenia; alcohol; PANSS; negative symptom; positive symptom; naltrexone; craving

Comorbid substance use disorders (SUDs) occur more frequently in patients with schizophrenia-spectrum disorders than in the population at large (Westermeyer, 2005). Nearly half of patients with schizophrenia have co-occurring SUDs, with the most commonly used substances being tobacco, alcohol and cannabis (Dixon, 1999). SUDs are known to adversely affect the clinical status of patients with schizophrenia and are associated with a variety of poor outcomes including increased suicide attempts and higher hospitalization rates (Westermeyer, 2005).

Given the high prevalence of SUDs among patients with schizophrenia- spectrum disorders, various theories have been proposed regarding the relationship between serious mental illness and substance use. For example, the common risk factor hypothesis suggests that individuals with schizophrenia are at greater risk for substance abuse due to a combination of factors shared between schizophrenia and SUDs, such as genetic variables, lower socioeconomic status, and cognitive deficits (Mueser et al, 1998). On the other hand, the self-medication theory proposes that substance use is an attempt to compensate for the symptoms of schizophrenia -- and in particular, the negative symptoms (Khantzian, 1997). Further specifying this concept, the reward circuitry dysfunction theory proposes that by acutely increasing mesolimbic dopamine levels, self-medication via substance use may ameliorate dysfunctional brain reward circuitry in schizophrenia (Green et al, 1999; Chambers et al, 2001; Nissel et al, 1995; Roth et al, 2005). An extension of this theory would be that patients with prominent negative symptoms such as anhedonia may be more likely to use substances in an attempt to restore normal hedonic tone. To date, only one study has attempted to test the effects of schizophrenia on alcohol consumption. D'Souza et al. (2006) reported enhanced sensitivity to the euphoric effects of alcohol in patients with schizophrenia as compared to normal controls. D'Souza also found that alcohol produced small transient increases in positive symptoms without affecting negative symptoms, therefore providing no support for the self-medication hypothesis. However, no subjects with alcohol abuse/dependence were included in their sample, and the report did not include analyses of differential responses to alcohol based on the positive or negative symptom patterns of the participants with schizophrenia.

Recent studies have investigated positive and negative schizophrenia symptom patterns in large naturalistic samples of patients with comorbid SUDs. A recent example is Margolese et al. (2006) who reported on a cohort of 147 outpatients, of whom 89% had schizophrenia/ schizoaffective disorder and roughly half had comorbid current or lifetime SUDs, with alcohol being the most prevalent substance used. Patients with SUD comorbidity had higher positive symptom baseline scores on the Positive and Negative Syndrome Scale [PANSS] (Kay et al, 1987) than patients without SUDs. Two new meta-analyses have attempted to summarize the relationship of schizophrenia symptoms to substance use. Potvin et al. (2005) examined 11 studies of patients with schizophrenia with or without concurrent SUD and concluded that patients with SUD had fewer negative symptoms than abstinent schizophrenia patients. Another recent meta-analysis by Talamo et al. (2006) included nine studies (of which only one study, with 54 subjects, overlapped with the Potvin analysis) encompassing 725 patients with schizophrenia of whom nearly half had substance use disorders (most often involving alcohol, followed by cannabis and cocaine). Talamo et al. found that patients with comorbid SUDs had significantly higher PANSS positive and lower PANSS negative scores. In summary, these studies indicate that substance use disorders appear to be associated with higher levels of

positive symptoms and also with lower levels of negative symptoms. To our knowledge, no published reports are available regarding the relationship between positive and negative symptoms of schizophrenia and the reported level of alcohol, cannabis, and cocaine use, the amount of alcohol craving, and the amount of alcohol "high" (euphoria).

The goal of this report is to describe the relationship between alcohol, cannabis and cocaine use and symptoms of schizophrenia in a cohort of treatment-seeking patients with schizophrenia and alcohol dependence entering a clinical trial of naltrexone pharmacotherapy. Specifically, we present data on the relationship of schizophrenia symptom severity to the levels of alcohol, cocaine and cannabis use and to the levels of alcohol craving and intoxication. We also present an analysis of the specific negative symptoms that appear to be associated with varying levels alcohol use, craving, and euphoria or "high".

2. Methods

2.1. Participants

We report on the first 80 participants entering a NIAAA-funded double-blind, placebo-controlled clinical trial of directly monitored oral naltrexone for alcohol use disorders in schizophrenia (Batki, et al, 2007). All participants were outpatients with schizophrenia or schizoaffective disorder and with co-occurring alcohol dependence or abuse who provided written informed consent approved by the SUNY Upstate Medical University Institutional Review Board. They were recruited from community mental health clinics in Syracuse, New York. All participants were confirmed to be enrolled in ongoing outpatient psychiatric treatment and to be prescribed antipsychotic medications by their clinical treatment providers. Data were collected from November 2003 to August 2007.

2.2. Procedure

The study consisted of a screening phase, followed by a 12-week treatment phase that involved three visits per week for directly monitored administration of oral naltrexone or placebo plus weekly motivational counseling. The present analysis examines only the baseline data collected during the screening phase.

2.3. Measures

Baseline psychiatric measures included in this report are the Structured Clinical Interview for DSM-IV Axis I disorders [SCID-IV] (Psychotic, Mood, and Substance Use Modules) (First et al, 2002); PANSS; Calgary Depression Scale for Schizophrenia [CDSS] (Addington et al., 1993); and Global Assessment of Functioning (GAF) Scale (Luborsky, 1962). Alcohol-related measures reported here included the Time Line Follow Back [TLFB] (Sobell and Sobell, 1992) adapted to include cannabis and cocaine use in addition to alcohol; the Alcohol Severity Composite portion of the Addiction Severity Index [ASI] (McLellan et al., 1992); and a 100 mm visual analog scale (VAS) for level of alcohol craving (Anton et al, 1996) over the past week; a 100 mm VAS for self-report of the quality of alcohol "high" (Batki et al. 2001) experienced when drinking alcohol. A concomitant medication form was used to gather current medication information from the participant and from review of the participant's clinical records.

2.4. Data Analysis

Data was analyzed using SPSS (v15.1) for Windows. The Spearman rho coefficient was used for pairwise correlations.

3. Results

3.1. Sample description

Table 1 presents the demographic characteristics of the 80 participants. Overall, the sample was primarily male, single, middle-aged, and Caucasian. Participants had low income and almost all were unemployed, with two-thirds receiving disability payments.

Table 2 describes the psychiatric characteristics of the sample. Slightly more than half were diagnosed with schizophrenia, and the remainder with schizoaffective disorder. Over 90% were prescribed atypical antipsychotics, either alone or in combination with other agents; almost half were also prescribed antidepressants. This sample of outpatients had relatively low PANSS positive and negative symptoms compared to the inpatient standard used as a normative group in PANSS manual (Kay et al, 2006) and had low levels of depressive symptoms on the CDSS. Mean GAF score reflected some impairment of reality testing or communication, or major impairment in several areas of functioning such as work or school, family relations, judgment, thinking or mood.

Table 3 presents the alcohol, cannabis, and cocaine diagnoses; levels of use; and other substance use characteristics. Almost all (95%) had a diagnosis of current alcohol dependence; the remaining participants were diagnosed with alcohol abuse. On average, participants consumed 19 standard drinks per week and reported moderate levels of alcohol craving and quality of alcohol “high” (euphoria) when drinking. Over one third (34%) were also diagnosed with current cannabis abuse/dependence and nearly one third (31%) with current cocaine abuse/dependence. Baseline urine drug testing was positive for tetrahydrocannabinol (THC) in 31% and for cocaine in 25% of participants.

3.2 Correlational analysis

We performed pairwise correlations between PANSS scores (Positive, Negative, General, and Composite) and the following alcohol/substance use measures: TLFB number of days of drinking and number of heavy drinking days in the baseline week, number of standard drinks and drinks per drinking day in the baseline week, amount of alcohol craving and quality of alcohol “high”, ASI Alcohol Composite score, ASI number of days of drinking and drinking to intoxication in the baseline month, and ASI number of days of cannabis and cocaine use in the baseline month.

Table 4 presents Spearman rho correlations between PANSS scores and measures of substance use. PANSS Negative scores correlated inversely with ASI alcohol severity (rho = −.26; $p < 0.05$), alcohol craving (rho = −.30; $p<0.01$), quality of alcohol “high” (rho = −.27; $p<.05$), and with days of cannabis use (rho = −.30; $p<0.01$). PANSS Composite scores -- reflective of predominance of positive symptoms of schizophrenia over negative symptoms -- were associated with greater alcohol craving and more days of cannabis use (rho=.26; $p<0.01$ and rho=.31, $p<0.05$, respectively). PANSS General scores were also associated with greater alcohol craving (rho=.25; $p<0.05$).

In an effort to further explore the possible relationship of PANSS Negative symptoms to alcohol and substance use, we carried out an exploratory analysis of pairwise correlations between PANSS Negative Scale items and substance use variables. Table 5 presents these exploratory correlations, which have not been corrected for multiple comparisons. Of the seven items in the PANSS Negative Scale, four appeared to be significantly negatively correlated with alcohol variables in this preliminary analysis. Greater “passive/apathetic social withdrawal” (consisting of the inability to engage in social interaction and/or a lack of initiative for such) was significantly associated with lower ASI alcohol severity, fewer drinking days in the past week and past month, and less craving for alcohol. More severe “blunted affect” was

significantly associated with less alcohol craving. Greater “difficulty in abstract thinking” and “stereotyped thinking” were both significantly associated with lower quality of alcohol “high” when drinking. Several items in the PANSS Negative Scale were also associated with less cannabis use. More severe “blunted affect”, greater “difficulty in abstract thinking”, and greater “lack of spontaneity and flow of conversation” were each associated with fewer days of cannabis use in the past month.

4. Discussion

This report examines the relationship between positive and negative symptoms of schizophrenia and alcohol use variables in a cohort of treatment-seeking alcohol dependent patients with schizophrenia or schizoaffective disorder. The strengths of the study are the use of structured diagnostic and rating instruments, and a variety of detailed alcohol and drug use measures not utilized in previous reports, including amount and frequency of alcohol use, levels of alcohol craving and quality of alcohol intoxication or “high”, and frequency of cannabis and cocaine use.

Our findings in a sample of alcohol dependent schizophrenia-spectrum patients add to what has previously been shown regarding the relationship of negative symptoms of schizophrenia to alcohol and drug use. Our results support previous findings indicating that negative symptoms of schizophrenia are associated with lower alcohol use severity. We have provided new details regarding the relationship between schizophrenia symptoms and amount and frequency of alcohol and other substance use and we have also shown that negative symptoms of schizophrenia appear to be associated with less alcohol use, lower levels of alcohol craving and lower amount of reported alcohol “high” (euphoria).

Participants with a preponderance of positive over negative symptoms, as reflected by higher PANSS Composite scores were found to have higher craving for alcohol. This finding is interesting, taking into account that in our sample, positive symptoms alone were not significantly associated with any alcohol or drug use variables. While there are significant associations between schizophrenia symptom clusters and alcohol use, these correlations do not indicate the directionality of the relationship. One may hypothesize, however, that patients with a preponderance of positive symptom severity may be attempting to use alcohol to alleviate psychotic symptoms and/or to reduce the effect of antipsychotic medication, although the human laboratory study of D’Souza et al. (2006) did not support this conclusion. Conversely, alcohol use itself may lead to the exacerbation of positive symptoms, as was suggested by D’Souza’s findings. Our findings do not lend support to the self-medication hypothesis which would predict that negative symptoms may be correlated with greater substance use in an effort to compensate for blunted brain reward. On the contrary, our findings may suggest that negative symptoms and possibly impaired brain reward system functioning may be associated with reduced ability to experience alcohol-mediated reward, as reflected by reduced quality of alcohol “high”, and less alcohol craving and consumption – even among patients with alcohol use disorders. Reduced alcohol and cannabis use may also reflect impairments in the ability to procure alcohol and drugs due to the social and cognitive functioning deficits associated with negative symptoms.

In an exploratory analysis, we examined how specific negative symptoms may relate to various alcohol use variables and found that several domains of symptoms covering affect, social behavior, and cognition may be involved. Blunted affect, social withdrawal, difficulties in abstract thinking, and stereotyped thinking were variously associated with less alcohol craving, less frequent drinking, or lower reported quality of alcohol “high”. Difficulties with abstract thinking, blunted affect, and lack of spontaneity, were also associated with less cannabis use.

4.1. Limitations

Limitations of this study include a relatively small sample size consisting only of participants who sought alcohol treatment through a clinical trial, possibly limiting our ability to generalize from the findings. The focus of the analysis is on baseline measures only, thereby precluding any analysis of the directionality of the relationships between alcohol use and PANSS symptoms presented here. We did not take antipsychotic medications into account in our analyses, and it is possible that amounts and types of typical or atypical antipsychotics may affect alcohol and substance use. On the other hand, almost all of the participants were receiving atypicals, and D'Souza et al. (2006) found no differential effect of atypical versus typical antipsychotic use on alcohol effects. Another limitation of our analysis is that there is some overlap between our measures of alcohol use – two items on the TLFB measuring frequency of drinking and heavy drinking per week overlap somewhat with two items on the ASI which measure the frequency of alcohol use alcohol intoxication in the past 30 days. Moreover, our exploratory analysis of the relationship of specific PANSS Negative Scale items to substance use variables is preliminary in nature and was not corrected for multiple comparisons. Therefore any conclusions drawn from these exploratory analyses are tentative, and were included in order to stimulate the development of further research into these relationships.

4.2. Future Research

More effort may be needed to address alcohol and other substance use in alcohol-dependent patients with schizophrenia if they have more severe positive symptoms, as these symptoms may indicate vulnerability to higher levels of substance use and therefore greater potential harm. Future studies should continue exploring the relationship between alcohol use variables such as craving and level of intoxication and psychiatric symptom severity. Further clarifying the relationship of schizophrenia symptom patterns to alcohol craving, use, and intoxication could help increase understanding of the reasons for drinking and substance use in this patient population and thereby lead to improvements in treatment.

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Table 1

Sociodemographic characteristics of study participants (N = 80)

Variable	% (N)
Male	73% (58)
Race	
Caucasian	45% (36)
African-American	39% (31)
Mixed	13% (10)
Other	3% (3)
Ethnicity	
Non-Hispanic	94% (75)
Hispanic	6% (5)
Married	8% (6)
Live independently	73% (58)
Income source	
Disability	66% (53)
Public Assistance/Welfare	18% (14)
Other/do not know	5% (4)
Employment	5% (4)
No income	6% (5)
Employed	9% (7)
Variable	**Mean [SD]**
Age	42 [9]
Education	12 [3]

Table 2

Clinical characteristics of study participants (N = 80)

	%	N	Mean	SD	Possible range	Percentile & interpretation
Diagnosis						
Schizophrenia	55%	44				
Schizoaffective Disorder	45%	36				
GAF			40	7	0–100	Some impairment of reality testing and/or communication
Baseline psychiatric medications						
Typical Antipsychotic only	9%	7				
Atypical antipsychotic only	80%	64				
Typical and Atypical	11%	9				
Mood stabilizers	29%	23				
Antidepressants	55%	44				
Antianxiety medication	31%	25				
PANSS[a]						
Positive			15	5	7–49	21, Low
Negative			13	5	7–49	8, Low
General			32	7	16–112	21, Low
Composite			2	8	−42 – +42	69, Average
CDSS[b]			5	4	0 – 27	74% specificity, 100 % sensitivity

[a]The PANSS normative group includes 240 inpatient individuals with schizophrenia. On the PANSS Positive scale, the mean score of 15 corresponds to the 21st percentile (Low range). These results indicate that 21 % of patients in the PANSS inpatient normative group would score below our sample on this item. Our sample falls within the Low range of positive symptomatology. As compared to the normative group of inpatients, our outpatient sample exhibits a low level of positive symptoms. The same logic applies to the PANSS negative, general, and composite group.

[b]Our sample had a mean score of 5, which indicates a low level of depressive symptoms. The score of 5 yields 74% specificity (high accuracy in terms of discriminating depressed versus non-depressed participants) and 100 % sensitivity (100% accuracy in terms of detecting depression in participants) (Addington et al., 1993).

GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; CDSS = Calgary Depression Scale for Schizophrenia

Table 3

Alcohol and Other Substance Use Characteristics of Study Participants

	%	N
SCID DSM-IV Diagnosis		
Alcohol		
Abuse	5	4
Dependence	95	76
Cannabis		
Abuse/Dependence	34	27
Cocaine		
Abuse/Dependence	31	25

	Mean	SD	Median	IQR (25 –75)	Possible range
ASI					
Alcohol Composite	.53	.21	.54	.39 – .69	0 – 1
Days of drinking/30 days (N=80)	14.9	8.7	14.0	7.0 – 22.5	0–30
Days of drinking to intoxication/30 days (N=80)	13.6	9.2	12.0	5.3 – 20.8	0–30
Days of cocaine use/30 days (N=25 cocaine users)	2.1	4.7	0.0	0–2.0	0–30
Days of cannabis use/30 days (N=40 cannabis users)	6.2	9.7	0.5	0–20.0	0–30
TLFB (baseline week)					
No. of drinking days/wk(N=80)	3.1	2.4	3.0	1 – 5	0–7
No. of drinks per week (N=80)	31.5	36.5	19.4	2.7 – 48.6	n/a
No. of heavy drinking days/week (N=80)	2.1	2.3	1	0 – 4	0–7
No. of drinks per drinking day (N=63 alcohol users in past week)	10.8	11.7	8.4	4.4 – 13.3	n/a
Reported Alcohol Craving (N=80)	50.8	31.1	50.0	26.3 – 79.0	0–100
Reported Quality of Alcohol "High" (N=63 alcohol users in past week)	51.1	26.4	54.0	34.5– 70.0	0–100

IQR = Interquartile range

SCID= Structured Clinical Interview for DSM-IV

ASI = Addiction Severity Index. Higher number indicates higher severity.

TLFB = Timeline Followback

Table 4

Spearman rho Correlations among PANSS scores and substance use variables

(N = 80 except for TLFB Drinks per drinking day and Quality of "High", for which Ns = 63)

	PANSS scores			
	Positive	**Negative**	**General**	**Composite**
ASI Alcohol Composite	.04	**−.26(*)**	−.09	.12
ASI Drinking Days	.09	−.18	−.12	.15
ASI Drinking to Intoxication days	.06	−.16	−.14	.13
ASI: Cocaine use days	.00	.02	−.04	.01
ASI: Cannabis Use Days	.12	**−.30(**)**	.08	**.31(**)**
TLFB Drinking days	.02	−.14	−.17	.09
TLFB Heavy drinking days	−.03	−.12	−.14	.04
Total Drinks in baseline week	−.00	−.09	−.08	.03
Drinks per Drinking Day	.07	−.08	−.06	−.03
Alcohol Craving	.13	**−.30(**)**	**.25(*)**	**.26(*)**
Quality of Alcohol "High"	.11	**−.28(*)**	.14	.17

ASI = Addiction Severity Index (time frame: last 30 days)

TLFB = Timeline Followback (time frame: last 7 days

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 5

Spearman rho correlations among PANSS Negative Scale items and substance use variables

(N = 80 except for TLFB Drinks per drinking day and Quality of "High", for which Ns = 63)

	Blunted Affect	Emotional Withdrawal	Poor Rapport	Passive apathetic social withdrawal	Abstract thinking	Lack of spontaneity	Stereotyped thinking
ASI Alcohol Composite Score	−.202	.056	−.066	**−.32****	−.219	−.033	−.121
ASI: Drinking days in past 30	−.157	.034	−.044	**−.22***	−.184	−.076	.018
ASI: Drinking to Intoxication days in past 30	−.120	.083	−.043	−.145	−.206	−.067	−.026
ASI: Cocaine use days in past 30	.001	−.049	.022	.025	.158	.004	−.194
ASI: Cannabis use days in past 30	**−.36****	−.082	−.166	−.149	**−.23***	**−.24***	−.088
TLFB±: Total Drinks per week	−.014	−.035	.042	−.168	−.011	−.007	−.064
TLFB: Number of drinking days per week	.043	−.102	−.053	**−.26***	−.039	−.084	−.007
TLFB: number of heavy drinking days per week	.036	−.028	.019	−.164	−.108	−.062	−.081
TLFB: Drinks per drinking day	−.159	.139	.102	−.013	.062	.046	−.131
Amount of Craving	**−.36****	−.070	−.214	**−.30****	−.130	−.202	.043
Quality of "High"	−.175	−.060	−.059	−.211	**−.270***	−.054	**−.292***

ASI = Addiction Severity Index (time frame: last 30 days)

TLFB = Timeline Followback. (time frame: last 7 days

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).