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Predictors of Smoking Severity in Patients with Schizophrenia and Alcohol Use Disorders

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Abstract

The goal of the present study was to identify predictors of smoking severity in patients with schizophrenia and co-occurring alcohol use disorders (AUD). Our hypothesis was that negative symptoms of schizophrenia, severity of depression, male gender, drinking severity and recreational drug use were associated with increased smoking. Clinical data, including demographic variables, alcohol and substance use severity, psychiatric medications, severity of depression, positive and negative symptoms of schizophrenia were analyzed in a cohort of 90 patients with schizophrenia or schizoaffective disorder and AUD. 88% of participants were smokers; they smoked an average of 15 cigarettes/day. Zero-inflated negative binomial regression analyses demonstrated that alcohol use severity, gender and severity of negative symptoms were not predictive of the number of cigarettes smoked. Smoking severity was positively related to Caucasian race, psychosis severity (PANSS general score) and medications (conventional antipsychotics). Subjects, who used recreational drugs, smoked less. In summary, severe, treatment resistant schizophrenia, and conventional antipsychotic treatment is associated with heavy smoking in patients with schizophrenia and AUD regardless of gender, or alcohol use.

INTRODUCTION

Cigarette smoking in schizophrenia has been a major challenge for treatment providers over the past decades. The prevalence of cigarette smoking is higher in patients with schizophrenia compared to the general population and to mentally ill patients worldwide.¹ Most patients with schizophrenia start smoking before the onset of psychosis, and inhale more deeply.² Patients with schizophrenia are less likely to quit smoking,^{1,3–5} and they may be at greater risk of smoking-related morbidity and mortality.⁶

The strong association between nicotine dependence and schizophrenia is not well understood. Negative symptoms of schizophrenia (especially passive withdrawal and social

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DECLARATION OF INTEREST

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avoidance) were found to be associated with increased smoking.² Smoking temporarily improves negative symptoms and attention in patients with schizophrenia⁷⁻⁹ and reduces sensory-gating deficits.¹⁰⁻¹¹ Based on these findings our hypothesis was that smoking severity will be associated with the severity of negative symptoms in patients with schizophrenia and AUD.

Negative symptoms of schizophrenia (especially difficulty in abstract thinking) are associated with cognitive impairment (impaired memory and attention).¹² Treatment with conventional and depot antipsychotics is also associated with heavy smoking and negative symptoms.¹³⁻¹⁶ It is not clear, whether genetic predisposition, psychosis severity, recreational drug use or psychiatric medications are responsible for the heavy smoking in schizophrenia.

Over one-third of patients with schizophrenia meet criteria for an alcohol use disorder (AUD) – more than three times the prevalence in the population at large.¹⁷⁻¹⁸ Smoking and alcohol use are frequently associated with one another, and may both influence, or be influenced by, psychiatric symptoms. Male gender is associated with heavy drinking and higher prevalence of substance abuse and dependence.¹⁷ Depression is associated with smoking and alcohol use, especially in women.¹⁹⁻²⁰ Our hypothesis was that severity of depression, male gender, drinking severity and recreational drug use were associated with increased smoking. The goal of the present study was to identify possible predictors of smoking severity in a research cohort of patients with schizophrenia or schizoaffective disorder and co-occurring AUDs, focusing on the possible influence of demographic variables (age, gender, race), co-occurring alcohol and substance use, severity of psychiatric symptoms (depression and psychosis), and psychiatric medications (conventional and atypical antipsychotics).

METHODS

PARTICIPANTS

Clinical data from 90 participants enrolled in an NIAAA-funded, controlled trial of directly monitored naltrexone treatment for AUD in schizophrenia (ClinicalTrials.gov identifier NCT00145847)²¹ were analyzed. Participants were outpatients with schizophrenia or schizoaffective disorder with co-occurring alcohol dependence or abuse. They were recruited from community mental health clinics in Syracuse, New York and provided written informed consent. Patients with opioid abuse or dependence were excluded, but other drug use was allowed. All participants were prescribed antipsychotics. The present analysis included only the baseline data collected during the screening phase prior to initiation of naltrexone treatment for AUDs.

MEASURES OF ALCOHOL AND SUBSTANCE USE

Alcohol and substance use were assessed with biological measures {breathalyzer, urine toxicology screen}, self-report {the Addiction Severity Index (ASI),²² Timeline Follow-Back (TLFB)²³}, and diagnostic interview with the Structured Clinical Interview for DSM-IV (SCID).²⁴ The number of cigarettes smoked was recorded every day for 30 days using the TLFB. Urine toxicology screen was performed to check for cocaine, opioid, metamphetamine, cannabis and amphetamine use. Patients with opioid abuse or dependence were excluded from the study.

MEASURES OF PSYCHIATRIC SEVERITY

Schizophrenia symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS).²⁵ Diagnosis of schizophrenia vs. schizoaffective disorder was determined using

the SCID. Depression was assessed with the Calgary Depression Scale for Schizophrenia [CDSS].²⁶ A Global Assessment of Functioning (GAF) score was also determined.²⁷

DEMOGRAPHIC VARIABLES

Baseline demographic data included age, gender, race, ethnicity, monthly income, level of education, marital and employment status.

STATISTICAL ANALYSES

Statistical analyses included all 90 patients; statistical modeling was done with Stata Statistical Software (version 11.1, College Station, TX: StataCorp LP.) and SPSS for Windows, (version 15.0, Chicago: SPSS Inc.) All tests employed two-tailed $\alpha = .05$, and statistical assumptions were tested in concert with the techniques employed

Because our dependent variable (number of cigarettes smoked) is non-continuous and included excess zero counts, we utilized zero-inflated negative binomial regression (ZINB) to assess the contribution of several predictors on the number of cigarettes smoked. Zero-inflation models assess the contribution that predictors make to either the zero-inflated portion of the model (which in our case was predicting the likelihood of choosing not to smoke cigarettes) and/or to the non-inflated part of the model (interpreted as a typical ordinary least squares regression analysis, predicting the actual number of cigarettes smoked).

We assessed the contributions of age, gender, race (Caucasian vs. not), number of drinking days per month, use of recreational drugs (yes/no), diagnosis (schizophrenia vs. schizoaffective disorder), depression severity (Calgary score), psychosis severity (PANSS positive, PANSS negative and PANSS general score) and type of antipsychotic treatment (conventional, atypical or both) in the non-inflated part of our model. Use of recreational drugs (yes/no), Calgary depression scores and PANSS psychosis severity scores were also used as predictors in the inflation portion of our model.

RESULTS

Demographic data, psychiatric diagnoses and symptom severity, alcohol and substance use are summarized in Table 1.

The majority of participants were middle-aged, male, non-Caucasian, single, low-income, unemployed and supported on welfare or disability payments. Half of the patients were diagnosed with schizophrenia, the remainder with schizoaffective disorder. Mean GAF score reflected some impairment of reality testing or communication, or major impairment in several areas of functioning. PANSS positive and negative symptoms were relatively low compared to the inpatient standard used as a normative group in PANSS manual.²⁵

Alcohol use disorder consisted of dependence in 95% and abuse in 5% of participants. Baseline alcohol use averaged 4 days per week and 11 drinks per drinking day. 88% of participants (79 out of 90) were daily smokers; they smoked an average of 15 cigarettes per day. Sixty-two patients (69%) used other drugs occasionally, including marijuana (42 patients, 47%), cocaine (29 patients, 32%), sedatives (10 patients, 11%) opioids (6 patients, 7%) and metamphetamine (2 patients, 2%).

Most patients were treated with atypical antipsychotics (see Table 1). Nine patients (10%) were prescribed both conventional and atypical antipsychotics. Seventeen patients (19%) were treated with conventional antipsychotics. Antidepressants, mood stabilizers and sedatives were also used in combination with antipsychotics.

Results of zero-inflated negative binomial (ZINB) regression analyses are shown in Table 2. Individual ZINB coefficients and associated p-values indicated that Caucasian race was positively associated with smoking severity ($b=0.405$, $p<0.01$). PANSS general score was also positively associated with the number of cigarettes smoked ($b=0.029$, $p<0.03$). Patients on atypical antipsychotic medications ($N=82$) smoked less than patients on conventional antipsychotic medications ($b=-0.392$, $p<0.04$). The use of recreational drugs was shown to have a negative association with the number of cigarettes smoked ($b=-0.408$, $p<0.01$), meaning that fewer cigarettes were reported for those using recreational drugs. Interestingly, recreational drug use was also marginally significant in its contribution to zero-inflation ($b=-1.412$, $p=0.053$), indicating, that those who used recreational drugs were less likely to report zero cigarettes (less likely to be non-smokers).

In contrast to previous studies,^{19,20} there was no association between smoking, gender and alcohol use severity in our cohort of patients. Smoking severity was not associated with scores on the Calgary Depression Scale for Schizophrenia, or psychiatric diagnosis (schizophrenia vs. schizoaffective disorder).

CONCLUSIONS

The goal of the present study was to identify possible predictors of smoking severity in patients with schizophrenia or schizoaffective disorder and co-occurring AUDs. Our hypothesis was that severity of negative symptoms, severity of depression, male gender, drinking severity and other drug use were associated with increased smoking. In contrast, we found, that smoking severity was independent of gender and alcohol use severity, but it was positively related to Caucasian race, psychosis severity (PANSS general score) and conventional antipsychotic medications. The prevalence of smoking (88%) in our sample of patients with co-occurring schizophrenia and alcohol dependence was at the higher end of previously reported ranges of smoking rates, and markedly higher than the reported rate for patients with schizophrenia alone (62%).¹ Margolese et al.²⁸ found similar (89%) smoking rate in patients with schizophrenia and co-occurring substance use disorders. In contrast to patients without AUD,^{2,29} negative symptoms of schizophrenia (e.g. passive withdrawal and social avoidance) were not associated with increased smoking in our AUD sample, possibly because alcohol and other drug use (e.g. cocaine, marijuana) decreased PANSS negative scores.²⁸

Surprisingly, the use of recreational drugs was associated with less smoking in our cohort. One possible explanation is that subjects, who smoked marijuana, smoked less cigarettes. Further studies are needed to test this hypothesis – our present study was not powered to detect differences in recreational drug use. On the other hand, we found, that subjects, who used recreational drugs were less likely to be non-smokers. This marginally significant finding supports our original hypothesis, that smoking status is associated with recreational drug use.

There is an association between depression and smoking¹⁹ as well as depression and alcohol use²⁰ in the general population. The lack of association between smoking severity and the Calgary Depression Score was an unexpected finding in patients with schizophrenia and AUD. Literature on this subject is very limited. Garpegui et al.²⁹ described a cheerfulness effect and a calming effect of smoking in patients with schizophrenia. Further studies are needed to understand the role that depression plays in smoking in adults with schizophrenia.

Smoking severity in patients with schizophrenia may reflect both severity of psychosis and depression. Symptoms of “guilt feelings” “active social avoidance” and “disturbance of volition” may be associated with both psychosis and depression. This problem underlies the

importance of breaking down complex scales (like the PANSS general scale) to the level of individual symptoms to increase validity. To make this issue even more complicated, “Depression” is part of the PANSS general scale. Further studies are needed to determine whether severity of psychosis or depression is associated with heavy smoking in schizophrenia.

Patients treated with conventional, antipsychotics in our cohort smoked more than patients receiving atypical antipsychotic medications. These patients usually had a longstanding and severe illness; they were disabled, and did not improve on other psychotropic medications. This finding is consistent with other studies suggesting that patients treated with depot or conventional antipsychotics smoke more,^{13–16} and have more difficulties in quitting smoking.¹⁶ Since most patients start to smoke before the onset and treatment of schizophrenia,² it is likely, that fluphenazine or haloperidol therapy does not directly increase smoking, rather it is an indicator of psychosis severity, which is not reflected in PANSS positive scores due to the beneficial effect of treatment on positive symptoms (and less effect on general symptoms). These findings support the hypothesis, that smoking severity in schizophrenia is related to psychosis severity.

On the other hand, treatment with conventional antipsychotics may result in akathisia, parkinsonism and cognitive impairment. According to the “self medication hypothesis” patients may smoke more in order to relieve their negative and cognitive symptoms and to reduce akathisia and parkinsonism - by lowering antipsychotic medication levels.^{30,31} Smoking cigarettes may provide a sense of control over antipsychotic medication side effects in patients treated with depot antipsychotic medications, where noncompliance is not an option. In addition, cognitive impairment associated with severe negative symptoms and typical antipsychotic treatment may make it difficult for patients to limit their smoking.^{12,16}

Based on our findings, both psychosis severity and conventional antipsychotic medications are positively associated with smoking severity in schizophrenia and AUD. The fact, that most patients start to smoke before the onset of schizophrenia² makes it likely, that antipsychotics do not trigger nicotine dependence, but it cannot be ruled out, that they make it worse. Caucasian race is associated with increased smoking in both mentally ill and non-mentally ill populations.³² Further studies are needed to clarify whether Caucasians are more vulnerable to the harmful effects of nicotine.

Strengths of the present study are that it is naturalistic, having allowed inclusion of patients with multiple substance use and medical co-morbidities³³ with the use of standardized measures of psychosis severity and alcohol and other substance use. Limitations of the study include the small cohort (N=90), exclusion of opioid abuse/dependence and absence of objective smoking measures (e.g. cotinine, nicotine levels, breath CO testing) other than self-report via the Timeline Follow-Back procedure.

In summary, our results suggest that severe, treatment resistant schizophrenia is associated with heavy smoking in patients with schizophrenia and AUD regardless of gender, and alcohol use. Treatment with conventional antipsychotics significantly increases smoking severity. Further research is needed to clarify underlying causes of the observed strong association between psychosis and smoking severity.

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Table 1

Socio-demographic and clinical characteristics (N=90)

Demographics	Mean±SD	Range
Age (years)	41.8±9.0	22–59
Education (years)	11.6±2.3	6–17
Monthly Income (USD)	417 ± 351	0–1300
	No.	%
Gender: Male	64	71.1
Race:		
African American	37	41.1
Caucasian	38	42.2
Native American	2	2.2
Mixed/Other	13	14.4
Ethnicity: Hispanic	5	5.6
Employment: Currently employed/Student	9	10
Marital Status:		
Married	6	6.7
Never Married	58	64.4
Other (divorced, widowed)	25	27.8
Diagnosis	No.	%
Schizophrenia	45	50
Schizoaffective Disorder	45	50
Psychiatric Symptom Severity	Mean±SD	Range
GAF	39.6±6.6	30–60
PANSS General Score	32.4±7.1	20–49
PANSS Negative Symptoms	13.5±4.9	7–30
PANSS Positive Symptoms	15.4±5.2	7–31
Calgary Score	5.22±4.0	0–15
Addiction Severity	Mean±SD	Range
Number of cigarettes/week	108.6±98.7	0–510
Number of standard drinks/week	35.3±46.1	0–269
Number of drinking days/month	14.8±8.6	2–30
Cocaine use (days/month)	2.2±4.7	0–20
Marijuana use (days/month)	6.6±10.2	0–30
Sedative use (days/month)	2.5±8.0	0–30
Psychiatric Medications	No. of patients	%
Atypical antipsychotic drugs	82	91.1
Quetiapine	35	38.9
Risperidone	33	36.7
Olanzapine	18	20

Demographics	Mean±SD	Range
Aripiprazole	16	17.8
Ziprasidone	8	8.9
Clozapine	4	4.4
Conventional antipsychotic drugs	17	18.9
Fluphenazine decanoate	9	10
Haloperidol decanoate	5	5.5
Haloperidol	3	3.3
Antidepressants	49	54.4
SSRI's	27	30
Non-SSRI antidepressants	28	31.1
Bupropion	7	7.77
Mood stabilizers	26	28.9
Valproate	19	21.1
Lamotrigine/oxcarbazepine	7	7.77
Topiramate	2	2.2
Lithium	1	1.1
Benzodiazepines/sedatives	27	30
Other medications	20	22.2
Benzotropine	19	21.1
Atomoxetine	1	1.1

Table 2

Zero-inflated negative binomial regression model predicting Number of Cigarettes Smoked during the Baseline Week (N=90, $\chi^2(13)=78.81$, $p<0.001$)

	Coef	Robust SE	Significance	Lower 95% CI	Upper 95% CI
Number of Cigarettes smoked during Baseline Week					
Age	.00	.01	.601	-.01	.02
Male(vs. female)	.02	.14	.909	-.26	.29
Caucasian (vs. not)	.41	.13	.002	.14	.67
Use of Recreational Drugs (vs. not)	-.41	.15	.008	-.71	-.11
Calgary Depression Score	.00	.02	.958	-.04	.04
Schizophrenia Diagnosis (vs. Schizoaffective)	-.24	.15	.120	-.54	.06
PANSS Positive Score	-.01	.02	.489	-.04	.02
PANSS Negative Score	-.01	.02	.451	-.05	.02
PANSS General Score	.03	.01	.025	.00	.05
Atypical (versus Conventional) Antipsychotic	-.37	.19	.036	-.76	-.03
Both Atypical AND Conventional (versus Conventional) Antipsychotic	.15	.30	.622	-.44	.73
Zero-Inflation in Number of Cigarettes Smoked during Baseline Week					
Use of Recreational Drugs (vs. not)	-1.41	.73	.053	-2.84	.02
Calgary Score	.15	.11	.173	-.65	.36
PANSS Positive	-.00	.10	.998	-.19	.19
PANSS Negative	-.02	.10	.815	-.21	.17
PANSS General	-.08	.06	.166	-.21	.04