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Antipsychotic Treatment and Tobacco Craving in People with Schizophrenia

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Abstract

Objective—Nicotine dependence is high in schizophrenia, and craving is known to impact relapse during quit attempts.

Methods—We compared tobacco craving in smokers with schizophrenia treated with different antipsychotics.

Results—Mean craving scores were lowest in participants treated with first generation antipsychotics, although these differences were not statistically significant. Craving with clozapine was not lower than with other antipsychotics.

Conclusions—Further research is needed to determine if differences in craving exist between antipsychotic classes.

Keywords

Tobacco; craving; schizophrenia; antipsychotic

Introduction

Nicotine dependence is high in schizophrenia, nearly three times more prevalent than the general population (A. Baker et al., 2006; Chaves & Shirakawa, 2008; Herran et al., 2000; Moeller-Saxone, 2008; USDHHS, 2011). In smokers with schizophrenia, the risk of all-cause mortality is doubled and cardiovascular mortality risk is twelvefold higher than in nonsmokers (Kelly et al., 2011). Many factors influence smoking in this population (Winterer, 2010); however, predictors of smoking behavior in schizophrenia are not well established.

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Craving is a major contributor to smoking, and, importantly, is a predictor of relapse risk (Berlin, Singleton, & Heishman, 2013). Since craving may precede relapse, it can be advantageous as a screening tool for those attempting cessation. In addition, focusing on treatments aimed to reduce craving might lead to better therapeutic targets. A combination of cessation strategies may be associated with reduced relapse, primarily due to craving suppression (Bolt, Piper, Theobald, & Baker, 2012), so targeting craving may offer important gains in improving abstinence. The DSM-5 has included craving as a symptom in diagnosing substance use disorders, which may increase attention to craving research (T. B. Baker, Breslau, Covey, & Shiffman, 2012; Casey, Adamson, Shevlin, & McKinney, 2012; Hasin, 2012).

Most addictive drugs, including nicotine, enhance dopamine release in the mesolimbic “reward” pathway (Nestler, 2005). Nicotine then mediates reinforcement from smoking via dopaminergic transmission, which is significant in schizophrenia as dopamine-mediated responses to rewarding stimuli may be abnormal (Chau, Roth, & Green, 2004). This phenomenon, thought to be related to reward circuitry deficits, may be further complicated by the dopaminergic antagonism of antipsychotics. Together, these factors may affect craving and/or smoking behavior in smokers with schizophrenia.

Several previous studies have examined craving in smokers with schizophrenia. A review of these data did not indicate that smokers with schizophrenia experienced higher smoking urge levels than smokers without schizophrenia prior to or following smoking cues (Tidey & Williams, 2007). A more recent study, however, has demonstrated possible differences in craving and withdrawal symptoms between smokers with and without schizophrenia. During a 72-hour smoking abstinence period, smokers with schizophrenia reported more severe symptoms of tobacco craving and withdrawal compared to smokers without schizophrenia (Tidey, Colby, & Xavier, 2014). These findings reinforce that craving and smoking behaviors in persons with schizophrenia should continue to be explored.

Due to their effects on the dopaminergic neurotransmitter systems, antipsychotics likely impact craving and nicotine’s rewarding effects. Several antipsychotic medications have been studied for their effects on dependence, sometimes including craving, in non-schizophrenia samples for other substances of abuse, such as alcohol use disorder (Kishi, Sevy, Chekuri, & Correll, 2013; Martinotti et al., 2016), cocaine, or psychostimulant dependence (Indave, Minozzi, Pani, & Amato, 2016; Kishi, Matsuda, Iwata, & Correll, 2013). However, craving has not generally been the primary outcome measure in these studies. Within the tobacco-related literature, antipsychotic studies have primarily examined overall smoking behavior, not craving specifically. This may explain why findings have been mixed for smokers with schizophrenia. Antipsychotics differ in dopaminergic blockade and affinity for other receptors, and so may differ in effects on smoking behaviors and craving.

Several reports indicate that clozapine may be associated with decreased smoking (George, Sernyak, Ziedonis, & Woods, 1995; J. McEvoy et al., 1995) relative to haloperidol (McEvoy, Freudenreich, Levin, & Rose, 1995) and other first generation antipsychotics (FGA) (Frankenburg, Zanarini, Kando, & Centorrino, 1998; McEvoy, Freudenreich, & Wilson, 1999) or second-generation antipsychotics (SGA) (Combs & Advokat, 2000). Conversely,

other reports found no differences in plasma cotinine between smokers with schizophrenia treated with clozapine or haloperidol (de Leon, Armstrong, & Cozza, 2006). In another study (Barnes et al., 2006) found no difference in smoking for SGA-treated patients, although post hoc examination showed more heavy smoking in the FGA group compared with olanzapine or risperidone. Most of these studies were observational, secondary analyses and not designed to study craving or smoking in a controlled environment. Since measures of craving often do not correlate to cigarettes smoked daily and years of smoking (Donny, Griffin, Shiffman, & Sayette, 2008), specific focus on craving is necessary in tobacco research.

Thus, with the limited tobacco craving-focused research data available in schizophrenia, results thus far have been mixed, and investigations have included non-mentally ill smokers not chronically treated with antipsychotic medications in acute challenge studies to determine effect on cue-elicited craving. In these laboratory experiments, some data suggest decreased craving on antipsychotics, whereas other data suggest increased smoking behavior (Dawe, Gerada, Russell, & Gray, 1995) (Caskey, Jarvik, & Wirshing, 1999; J. McEvoy et al., 1995), (J. P. McEvoy et al., 1995; Procyshyn, Tse, Sin, & Flynn, 2002). Several studies have focused on craving with non-clozapine antipsychotics given acutely to healthy smokers. Olanzapine and aripiprazole have shown craving attenuation in acute treatment when administered to healthy smokers (Hutchison et al., 2004; Yu Liu et al., 2010; Y. Liu et al., 2009). It is difficult to generalize these results to smokers with schizophrenia who undergo chronic treatment with these agents and have potentially differing circuitry, and studies reflect this complicated picture, with outcomes like dependence, expired carbon monoxide (CO) levels, and smoking speed showing various outcomes (Hutchison et al., 2004; Yu Liu et al., 2010; Y. Liu et al., 2009). Moreover, most of these studies failed to examine craving as an outcome, leaving a large gap in the literature.

The purpose of this study was to examine craving 15 minutes after smoking a cigarette in smokers with schizophrenia treated with clozapine compared to those treated with other antipsychotics. Five groups of smokers with schizophrenia were included: those treated with clozapine, olanzapine, risperidone, FGA, or multiple antipsychotics.

2. Methods

Persons with DSM-IV schizophrenia (age 18–65) smoking at least 5 cigarettes daily and with breath CO of at least 8 parts per million were enrolled. Participants were recruited through the Maryland Psychiatric Research Center and its affiliated network, advertising for smokers with schizophrenia in the Baltimore, MD area. Participants included in these analyses were stable antipsychotic-treated outpatients not actively undergoing cessation efforts. This study was conducted in accordance with the Declaration of Helsinki and approved by the University of Maryland-Baltimore, National Institute on Drug Abuse, and State of Maryland Department of Health and Mental Hygiene Institutional Review Boards. Fifty-nine participants gave informed consent after study education and were included in these analyses. The antipsychotic groups were clozapine ($N = 19$, alone or with other antipsychotics), olanzapine ($N = 9$), risperidone ($N = 9$), FGA ($N = 10$, chlopromazine,

haloperidol, loxapine, perphenazine), and combinations of nonclozapine antipsychotics ($N=12$, 5 SGA combinations and 7 SGA plus FGA combinations).

2.1 Smoking Assessments

The Fagerström Test for Nicotine Dependence (FTND) was used to evaluate nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Steinberg, Williams, Steinberg, Krejci, & Ziedonis, 2005). The Tobacco Craving Questionnaire-Short Form (TCQ-SF) (12-item) assesses four dimensions of tobacco craving: emotionality (anticipating relief from withdrawal symptoms or negative mood), expectancy (anticipating positive outcomes), compulsivity (lack of control over use), and purposefulness (intention/planning to smoke for positive outcomes) (Heishman, Singleton, & Pickworth, 2008). Breath carbon monoxide (CO) was also evaluated. The TCQ-SF and breath CO were assessed before and 15 minutes after the cigarette. Fifteen minutes was selected to create a standardized period to assess craving but not capture withdrawal phenomenon.

2.2 Procedures

The study consisted of one 2–3 hour visit. Participants completed assessments gathering demographics, smoking history/behavior, and nicotine dependence. This study is a secondary analysis of a larger study examining smoking craving between smokers with schizophrenia and healthy smokers (Kelly et al., 2012; Lo et al., 2011; Mackowick et al., 2012). This analysis will report the smoking characteristics of smokers with schizophrenia by antipsychotic group.

2.3 Statistical Analysis

Demographic/smoking characteristics between groups were compared using Student's T tests and Chi Square when appropriate. Analysis of variance (ANOVA) was performed to test for group differences. Group comparisons on craving 15 minutes post-smoking were analyzed using analysis of covariance (ANCOVA) adjusting for pre-smoking craving scores. Because of our initial focus on potential differential effects of clozapine, we performed post hoc comparisons to compare clozapine to each of the other groups. All tests were 2 sided with $\alpha = 0.05$; we also report p -values adjusted for multiple comparisons using the Benjamini-Hochberg (1995) False Discovery Rate (FDR) procedure.

3. RESULTS

3.1 Demographic information

Overall, mean age ($n = 59$) was 46.3 ± 10.2 , mean number of cigarettes smoked per day was 21.3 ± 11.6 , and mean age of first cigarette was 16.8 ± 5.6 . The mean overall FTND score was 5.4 ± 1.9 and baseline breath CO was 30.7 ± 20.5 . There were no group differences in gender, race, marital status, age, or education level. Number of cigarettes smoked daily, mean FTND scores, age at first use, and breath CO did not differ among groups (Table 1).

3.2 Tobacco Craving (Table 2)

Mean post-cigarette TCQ SF total scores were 48.9 ± 18.3 for clozapine, 48.8 ± 21.7 for olanzapine, 48.1 ± 17.8 for risperidone, 36.5 ± 20.1 for FGA, and 45.7 ± 21.3 for antipsychotic combination group ($F = 1.46$, $df = 4, 53$, $p = 0.23$). Pairwise comparisons between the FGA group and clozapine found significantly lower craving for FGA relative to clozapine (difference $\pm SE = -10.5 \pm 4.66$, $t = -2.25$, $p = 0.03$, FDR-adjusted p value = 0.19).

3.2.1 TCQ-SF Factors—Overall, the ANOVA showed no differences between groups in any of the four factors: emotionality ($F = 1.53$, $df = 4, 53$, $p = 0.21$), expectancy ($F = 2.1$, $df = 4, 53$, $p = 0.09$), compulsivity ($F = 0.36$, $df = 4, 53$, $p = 0.84$), and purposefulness ($F = 0.95$, $df = 4, 53$, $p = 0.44$). Exploratory pairwise comparisons with clozapine showed lower factor scores in the FGA group compared to clozapine for emotionality (difference $\pm SE = -3.70 \pm 1.64$, $t = -2.25$, $p = 0.03$, FDR-adjusted p -value = 0.19) and expectancy (difference $\pm SE = -4.28 \pm 1.75$, $t = -2.44$, $p = 0.018$, FDR-adjusted p -value = 0.19). Additionally, the expectancy factor was lower in the risperidone group vs. clozapine (difference $\pm SE = -3.71 \pm 1.83$, $t = -2.03$, $p = 0.048$, FDR-adjusted p -value = 0.24). There were no differences noted on the other TCQ-SF factors, nor were there any other post hoc differences from clozapine among antipsychotics.

4. DISCUSSION

In a cohort of smokers with schizophrenia, we found no overall difference in tobacco craving between antipsychotic groups, possibly due to small sample size and multiple groups. Upon direct comparison of FGA vs clozapine, FGA-treated participants tended to give lower craving scores than clozapine-treated participants. This finding needs replication in a larger study with sufficient power. Mean total craving scores were nearly identical in smokers with schizophrenia treated with clozapine, olanzapine or risperidone. Craving was most notably blunted in the FGA group in areas of emotionality and expectancy.

The tendency of lower craving with FGA compared to clozapine is worthy of discussion as this was of primary a priori interest. Our prior hypothesis, that craving would be reduced in participants treated with clozapine compared to other antipsychotics, based on clozapine's unique pharmacology (Procyshyn et al., 2002) and reports in previous studies of decreased tobacco use with clozapine, was not supported. However, craving did not differ among participants treated with clozapine versus other SGA antipsychotics in this cross-sectional study. We did have the unexpected results that smokers treated with FGA had the lowest craving scores among all the groups examined, although this result was not statistically significant after correction for multiple comparisons. Prior challenge studies testing haloperidol's effects on craving and smoking urge in healthy smokers have produced conflicting results. Smoking intensity and urge increased with haloperidol in several studies (Caskey et al., 1999) (Caskey et al., 2002) (Dawe et al., 1995) (Mahler & de Wit, 2005), but one study found smoking decreased (Brauer, Cramblett, Paxton, & Rose, 2001). Few comparisons are available to evaluate craving among antipsychotics in smokers with schizophrenia. Since FGA are generally more potent dopaminergic antagonists, it may be theorized that diminished craving with FGA may be related to blockade in reward pathways.

This is supported by the finding that haloperidol attenuates craving for other drugs like cocaine; reduced craving was found in both cocaine-using schizophrenia subjects (Sayers et al., 2005) and healthy cocaine-dependent inpatients (Berger et al., 1996). In our study, FGA were associated with lower scores in expectation/anticipation of benefits and withdrawal relief or negative symptoms.

Limitations of this study include observational and cross-sectional design, no random treatment assignments or control group, small sample sizes, and omission of other SGAs. In particular, this study is that this is a cross-sectional look at people with average ages in their 40s, recruited as active smokers. Ex-smokers were not eligible. If clozapine helped people quit, more people on clozapine would be ineligible for this study, and the smokers on clozapine would be those least susceptible to antismoking effects of clozapine, whether via craving or other pathways. Moreover, there were no statistically significant findings in the overall ANOVA comparing treatment groups, which may reflect small sample sizes and inadequate power. In addition, the absence of craving or smoking intensity differences among participants prescribed clozapine, olanzapine and risperidone, as well as higher craving in clozapine compared to the FGA group (pairwise comparisons), appears inconsistent from earlier reports that clozapine reduces smoking in persons with schizophrenia (George et al., 1995) (J. McEvoy et al., 1995). These results suggest further research in larger studies is required.

Craving has recently gained attention as a recommended target for new therapeutic options for addiction. This pilot study provides some of the first comparative data among several antipsychotics examining antipsychotic effects on tobacco craving. Further research to understand the complexity of craving and relapse will be important to validate the construct of craving as an outcome, and optimize smoking cessation strategies, which could have profound effects on improving long term morbidity and mortality.

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Table 1

Demographics and Clinical Information

Characteristic	Clozapine	Olanzapine	Risperidone	FGA	Two AP	Statistic
<i>N</i>	19	9	9	10	12	
Male	<i>N</i> = 14, 74%	<i>N</i> = 9, 100%	<i>N</i> = 7, 78%	<i>N</i> = 5, 50%	<i>N</i> = 9, 75%	($\chi^2 = 6.31$, <i>df</i> = 4, <i>p</i> = 0.18)
White	<i>N</i> = 12, 63%	<i>N</i> = 6, 67%	<i>N</i> = 4, 44%	<i>N</i> = 7, 70%	<i>N</i> = 6, 50%	($\chi^2 = 2.05$, <i>df</i> = 4, <i>p</i> = 0.73)
Single	<i>N</i> = 14, 74%	<i>N</i> = 7, 78%	<i>N</i> = 9, 100%	<i>N</i> = 7, 88%	<i>N</i> = 7, 58%	($\chi^2 = 5.70$, <i>df</i> = 4, <i>p</i> = 0.22)
Age (years)	45.8 ± 9.7	45.9 ± 13.4	42.2 ± 10.2	49.5 ± 6.6	48.0 ± 11.2	<i>F</i> = 0.69, <i>NDF</i> = 4, <i>DDF</i> = 54, <i>p</i> = 0.60
Education	12.2 ± 1.8	12.9 ± 1.4	12.7 ± 1.2	11.6 ± 2.6	12.1 ± 3.0	<i>F</i> = 0.49, <i>NDF</i> = 4, <i>DDF</i> = 52, <i>p</i> = 0.74
Number of cigarettes/day	20.1 ± 11.4	26.0 ± 17.9	20.8 ± 9.9	21.1 ± 12.8	20.4 ± 6.2	<i>F</i> = 0.42, <i>NDF</i> = 4, <i>DDF</i> = 54, <i>p</i> = 0.79
FTND	5.3 ± 1.5	5.7 ± 2.5	5.4 ± 2.3	5.6 ± 2.0	5.4 ± 2.1	<i>F</i> = 0.07, <i>NDF</i> = 4, <i>DDF</i> = 53, <i>p</i> = 0.99
Age at first cigarette use (years)	16.7 ± 4.7	15.6 ± 5.4	17.0 ± 3.0	16.4 ± 9.7	17.9 ± 4.2	<i>F</i> = 0.22, <i>NDF</i> = 4, <i>DDF</i> = 53, <i>p</i> = 0.92
Expired CO (ppm)	25.6 ± 13.5	36.9 ± 25.7	32.3 ± 14.6	27.6 ± 16.0	23.4 ± 11.4	<i>F</i> = 1.81, <i>NDF</i> = 4, <i>DDF</i> = 50, <i>p</i> = 0.14

Note. FGA= first generation antipsychotics

Two AP= two antipsychotics (not including clozapine)

CO = carbon monoxide

FTND = Fagerström Test for Nicotine Dependence

Table 2

Mean craving scores by antipsychotic group

		Clozapine (<i>n</i> = 19)	Olanzapine (<i>n</i> = 9)	Risperidone (<i>n</i> = 9)	FGA (<i>n</i> = 10)	Two AP (<i>n</i> = 12)	Overall ANCOVA
TCQ Total							
	Baseline	44.0 (16.2)	49.4 (21.6)	49.2 (16.7)	41.1 (21.3)	41.3 (21.3)	
	15 minutes post cigarette	48.9 (18.3)	48.8 (21.7)	48.1 (17.8)	36.5 (20.1)	45.7 (21.3)	
<i>F</i> = 1.46, <i>df</i> = 4, <i>p</i> = 0.23							
TCQ Factor 1 (Emotionality)							
	Baseline	9.1 (4.1)	12.1 (5.4)	11.2 (5.1)	9.2 (5.6)	8.8 (4.8)	
	15 minutes post cigarette	11.9 (5.2)	11.1 (5.7)	11.4 (5.0)	8.3 (6.2)	9.7 (4.7)	
<i>F</i> = 1.53, <i>df</i> = 4, <i>p</i> = 0.21							
TCQ Factor 2 (Expectancy)							
	Baseline	11.1 (4.8)	12.8 (5.5)	13.1 (5.5)	11.1 (5.6)	11.0 (6.1)	
	15 minutes post cigarette	13.6 (5.7)	13.9 (5.6)	11.3 (6.1)	9.3 (5.9)	12.5 (6.4)	
<i>F</i> = 2.10, <i>df</i> = 4, <i>p</i> = 0.09							
TCQ Factor 3 (Compulsivity)							
	Baseline	10.9 (5.4)	11.4 (6.4)	11.2 (4.2)	9.7 (6.6)	10.3 (5.8)	
	15 minutes post cigarette	10.7 (5.2)	11.3 (6.5)	11.6 (5.9)	8.4 (4.9)	10.6 (6.6)	
<i>F</i> = 0.36, <i>df</i> = 4, <i>p</i> = 0.84							
TCQ Factor 4 (Proposefulness)							
	Baseline	12.9 (5.4)	13.1 (5.4)	13.7 (5.5)	11.7 (5.9)	11.3 (6.2)	
	15 minutes post cigarette	12.7 (5.0)	12.4 (5.7)	13.8 (5.7)	10.5 (5.7)	5.6 (3.0)	
<i>F</i> = 0.95, <i>df</i> = 4, <i>p</i> = 0.44							

Note. TCQ= Tobacco Craving Questionnaire- Short Form

Pairwise comparisons between the FGA group and clozapine found significantly lower craving for FGA relative to clozapine (difference $\pm SE = -10.5 \pm 4.66$, $t = -2.25$, $p = 0.03$, FDR-adjusted p value = 0.19). Exploratory pairwise comparisons with clozapine showed lower emotionality factor with FGA (8.3 $\pm$ 6.2) vs. clozapine (11.9 $\pm$ 5.2) (difference $\pm SE = -3.70 \pm 1.64$, $t = -2.25$, $p = 0.03$, FDR-adjusted p value = 0.19). The expectancy factor was lower in the FGA group (9.3 $\pm$ 5.9) vs. clozapine (13.6 $\pm$ 5.7) (difference $\pm SE = -4.28 \pm 1.75$, $t = -2.44$, $p = 0.018$, FDR-adjusted p value = 0.19). Additionally, the expectancy factor was lower in the risperidone group (11.3 $\pm$ 6.1) vs. clozapine (13.6 $\pm$ 5.7) (difference $\pm SE = -3.71 \pm 1.83$, $t = -2.03$, $p = 0.048$, FDR-adjusted p value = 0.24). After adjustment for performing 20 pairwise comparisons, none of these were statistically significant (for $p < 0.05$).