

Potent Dopamine D₂ Antagonists Block the Reward-Enhancing Effects of Nicotine in Smokers With Schizophrenia

Alexis E. Whitton^{1,2}, Alan I. Green^{3,4}, Diego A. Pizzagalli^{1,2}, Robert M. Roth³, Jill M. Williams⁵, and Mary F. Brunette^{*,3}

¹Center for Depression, Anxiety, and Stress Research, McLean Hospital, Belmont, MA; ²Department of Psychiatry, Harvard Medical School, Boston, MA; ³Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH; ⁴Dartmouth Clinical and Translational Science Institute, Hanover, NH; ⁵Department of Psychiatry, Rutgers University, New Brunswick, NJ

*To whom correspondence should be addressed; Department of Psychiatry, Dartmouth-Hitchcock, 2 Pillsbury Street, Suite 40, Concord, NH 03301, US; tel: 603-229-5419, fax: 603-271-5262, e-mail: mary.f.brunette@hitchcock.org

Antipsychotics that are potent dopamine (DA) D₂ receptor antagonists have been linked to elevated levels of nicotine dependence in smokers with schizophrenia. Because activation of D₂ receptors mediates motivation for nicotine, we examined whether potent D₂ antagonists would diminish nicotine's ability to stimulate reward processing—a mechanism that may drive compensatory increases in smoking. Smokers with schizophrenia ($n = 184$) were recruited and stratified into medication groups based on D₂ receptor antagonist potency. The effects of smoking on reward function were assessed using a probabilistic reward task (PRT), administered pre- and post-smoking. The PRT used an asymmetrical reinforcement schedule to produce a behavioral response bias, previously found to increase under conditions (including smoking) that enhance mesolimbic DA signaling. Among the 98 participants with valid PRT data and pharmacotherapy that could be stratified into D₂ receptor antagonist potency, a *medication × smoking × block* interaction emerged ($P = .005$). Post-hoc tests revealed a *smoking × block* interaction only for those not taking potent D₂ antagonists ($P = .007$). This group exhibited smoking-related increases in response bias ($P < .001$) that were absent in those taking potent D₂ antagonists ($P > .05$). Our findings suggest that potent D₂ antagonists diminish the reward-enhancing effects of nicotine in smokers with schizophrenia. This may be a mechanism implicated in the increased rate of smoking often observed in patients prescribed these medications. These findings have important clinical implications for the treatment of nicotine dependence in schizophrenia.

Key words: antipsychotics/reward learning/nicotine dependence

Introduction

Nicotine use in individuals with schizophrenia is extremely common, with recent estimates indicating that 80% of individuals with this condition smoke.¹ Greater smoking in this population has been linked to worse symptoms,² susceptibility to respiratory and cardiovascular diseases, and early mortality;³ hence, reducing smoking in these patients is a key priority. Evidence suggests that patients taking first-generation antipsychotics, many of which produce potent dopamine (DA) D₂ receptor antagonism, experience greater difficulty quitting with evidence-based cessation treatment.^{4,5} Because these medications are foundational to the management of schizophrenia, an important question is whether DA D₂ receptor antagonists modulate nicotine's reinforcing effects.

Nicotine's addictive properties are driven in large part by activity within the mesolimbic DA reward system.^{6,7} Nicotine stimulates DA neurons via nicotinic acetylcholine receptors (nAChRs) in the ventral tegmental area, causing the release of DA into striatal synapses.^{8,9} Human positron emission tomography studies have shown evidence of acute increases in DA signaling in the ventral striatum following nicotine intake.¹⁰ Nicotine has been found to enhance reward processing on several paradigms in both animals¹¹ and humans,¹² and is associated with increased neural activation in key reward regions.¹³ Conversely, nicotine withdrawal has been linked to decreases in reward processing.¹⁴

Mesolimbic DA system dysfunction is central to the pathophysiology of schizophrenia,^{15,16} and may be a pathway through which comorbid schizophrenia and

nicotine dependence develops.¹⁷ Supporting this notion, deficits in reward learning—a process reliant on phasic striatal DA signaling¹⁸—is correlated with increased nicotine dependence in schizophrenia.¹⁹ Furthermore, the nAChR partial agonist varenicline has been shown to restore nicotine withdrawal-related deficits in reversal learning (a process that is also reliant on phasic striatal DA signaling)²⁰ in rodents,²¹ and has been found to improve cessation and prolong abstinence,²² and boost reward processing in patients with schizophrenia.²³

Central to reducing smoking rates in schizophrenia is understanding how antipsychotic medications moderate nicotine's rewarding effects. Evidence indicates that treatment with potent DA D₂ receptor antagonists increases smoking in individuals with schizophrenia.^{24–26} Although the precise mechanisms are unknown, potent DA D₂ receptor antagonists may diminish nicotine's ability to stimulate mesolimbic DA release, which may drive a compensatory increase in smoking to achieve the same level of stimulation. Supporting this, studies in psychiatrically healthy smokers show that pretreatment with the potent DA D₂ antagonist haloperidol resulted in increased blood plasma nicotine (due to greater smoking during a free smoking period) compared to placebo.²⁷ Pretreatment with haloperidol has also been linked to a faster rate of smoking and greater total puffing time than treatment with the DA agonist, bromocriptine.²⁸ Similarly, 8 weeks of haloperidol treatment has been linked to significant increases in nicotine dependence in individuals with schizophrenia.²⁶

Conversely, smoking reductions have been observed in patients treated with lower DA D₂ receptor affinity medications.^{26,29} Specifically, clozapine—a potent blocker of the serotonin 5-HT_{2A} receptor and the norepinephrine α₂ receptor, as well as a weak DA D₂ receptor antagonist³⁰—has been associated with reduced daily cigarette use.²⁹ Similarly, aripiprazole—a partial agonist at both pre- and post-synaptic DA D₂ and 5-HT_{1A} receptors—has been associated with reduced nicotine dependence compared to haloperidol.²⁶ Quetiapine is also of interest, given its broad spectrum of action, including weak DA D₂ receptor antagonism.³¹

Together, these findings suggest that potent DA D₂ receptor antagonists may reduce the effects of nicotine on reward processing in smokers with schizophrenia; however, no study to date has tested this hypothesis. We aimed to address this gap by examining the effects of smoking on reward learning, a key aspect of reward processing that is defined as the process by which behavior is modified as a function of prior reinforcement. Reward learning was assessed using a behavioral probabilistic reward task (PRT)³² that uses an asymmetrical reinforcement schedule to induce a response bias toward a more frequently rewarded (rich) stimulus. In healthy individuals, stimulants that increase phasic DA signaling—including nicotine—potentiated response bias.¹²

Individual differences in response bias have also been linked to DA release,³³ DA transporter binding,³⁴ and functional connectivity between key reward system nodes in nonsmokers.³⁴ Furthermore, response bias has been found to be inversely related to cigarette craving intensity in smokers.³⁵ Consistent with prior studies,¹² we predicted that individuals with schizophrenia would show greater response bias after smoking compared to following abstinence, but that this increase would be attenuated in individuals taking potent DA D₂ receptor antagonists.

Methods

Participants

Participants were 184 chronic tobacco smokers with schizophrenia (122 male) enrolled in a multisite smoking cessation study (Randomized Controlled Trial of a Motivational Decision Support System [RCTEDSS]; ClinicalTrials.gov #NCT02086162). The aim of this multisite study was to evaluate whether the use of a web-based decision support system resulted in higher rates of initiation of smoking cessation treatment compared to use of a computerized educational pamphlet. The primary outcomes of this study will be reported separately. To be eligible, participants had to be English speaking, daily smokers, with a diagnosis of schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV)³⁶ and stable in mental health treatment. Exclusion criteria were psychiatric instability (a score >75 on the Brief Psychiatric Rating Scale [BPRS]³⁷); current moderate/severe alcohol/drug dependence; pregnancy/breastfeeding.

Measures

Demographic and Clinical Assessments. Demographics and psychiatric history were assessed with a structured interview at baseline. Diagnosis of schizophrenia, schizoaffective disorder, and current drug/alcohol dependence was determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV). Psychotic symptom severity was assessed using the BPRS. All assessments were administered by trained interviewers.

Classification of Antipsychotic Medication. Current antipsychotic medications were obtained by self-report and confirmed by record review. Medications were classified into groups based on the potency with which they blocked the DA D₂ receptor. This classification was carried out based on a theoretical hypothesis that the relative potency of DA D₂ receptor antagonism might contribute to the reward-enhancing effects of nicotine in patients with schizophrenia. Medications known to be potent DA D₂ receptor antagonists included haloperidol, fluphenazine, chlorpromazine, risperidone, olanzapine,

and paliperidone.³⁸ Participants who were taking a combination of antipsychotics that included a potent D₂ receptor antagonist and other types of antipsychotics were included in this class. Medications were considered “non-potent DA D₂ antagonists” if they were known to have lower DA D₂ antagonism (clozapine and quetiapine)^{38–40} or DA D₂ partial agonism, resulting in a lack of “functional antagonism” at DA D₂ receptors (aripiprazole).^{41–44} Patients who were not taking antipsychotic medication were excluded, as were those taking lurasidone, due to its complex pharmacologic profile.

Measures of Nicotine Dependence. Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND),⁴⁵ and smoking urges were assessed using the Tiffany Questionnaire of Smoking Urges (QSU).⁴⁶ Both measures have been found to have adequate psychometric properties among smokers with schizophrenia.⁴⁷ Expired carbon monoxide (CO)—associated with greater levels of smoking⁴⁸—was obtained using a Smokerlyzer monitor (Bedfont Scientific).

Probabilistic Reward Task. To probe reward responsiveness, all participants completed the PRT.³² Rooted within signal detection theory, the PRT allows for an objective assessment of the propensity to modulate behavior based on prior reinforcement. The PRT consisted of schematic faces presented on a monitor, each with 2 eyes, a nose, and a horizontal line for a mouth. On each trial, a fixation cross appeared for 500 ms, followed by a mouthless face. After 500 ms, either a “short mouth” (10 mm) or “long mouth” (11 mm) was presented for 100 ms. Participants indicated via keypress whether the short or long mouth appeared. There were 2 blocks of 100 trials, and 40 correct trials in each block were followed by a monetary reward (Correct!! You won 20 cents). Long mouths and short mouths were presented at equal frequencies; however, unbeknownst to participants, one of the mouth lengths (the “rich stimulus”) was rewarded 3 times more frequently than the other mouth length (the “lean stimulus”). Participants were told to try and win as much money as possible, as they would be given the money that they earned. To avoid practice effects from pre- to post-smoking, 2 versions of the PRT were used—a version where the length of the mouth varied, and a version where the length of the nose varied, with different versions administered in a counterbalanced order across participants.

Procedure

Participants were recruited through flyers and clinician referral. After providing informed consent, demographic, smoking, diagnostic, and symptom information was collected. Eligible participants returned to do the PRT and other cognitive assessments. They were instructed to

smoke prior to the study visit. At the beginning of the visit, participants indicated that they had smoked within the past hour, which was confirmed with a breath CO sample ≥ 10 ppm. They then completed cognitive assessments, and after being abstinent for at least 1 hour, completed the PRT for the first time. They then smoked one of their own cigarettes over a period of 15 minutes. After this smoking period, a second breath CO sample was taken, and participants repeated a counterbalanced version of the PRT performed within 10 minutes of finishing smoking.

Data Reduction and Statistical Analyses

PRT Quality Assurance and Data Reduction

In line with prior PRT studies,^{32,49} data were subjected to quality control analyses that involved excluding trials with reaction times of less than 150 ms or greater than 2500 ms, and data from participants who had accuracy scores below 50% (indicative of below-chance level performance), or from participants who had more than 25% reaction time outlier trials. Next, signal detection analysis⁵⁰ was used to calculate response bias (the tendency to bias responding to the rich stimulus) and discriminability (the ability to accurately distinguish between the 2 mouth sizes), according to the following formulas:

$$\text{Response bias : } \log b = \frac{1}{2} \log \left(\frac{\text{Rich}_{\text{correct}} \times \text{Lean}_{\text{incorrect}}}{\text{Rich}_{\text{incorrect}} \times \text{Lean}_{\text{correct}}} \right)$$

$$\text{Discriminability : } \log d = \frac{1}{2} \log \left(\frac{\text{Rich}_{\text{correct}} \times \text{Lean}_{\text{correct}}}{\text{Rich}_{\text{incorrect}} \times \text{Lean}_{\text{incorrect}}} \right)$$

In accordance with recommendations,⁵¹ 0.5 was added to every cell of the detection matrix to allow for log-transformation of cells containing a zero.

Statistical Analysis

A repeated measures analysis of variance (ANOVA) with *medication* (D₂ antagonism+, D₂ antagonism–) as the between-subject factor, and *smoking* (pre-smoke, post-smoke) and *block* (block 1, block 2) as within-subject factors, was used to examine the degree to which the presence of potent D₂ receptor antagonists moderated the effects of smoking on response bias. Significant interaction effects were followed up with tests of simple effects. Furthermore, bivariate Pearson correlations were used to examine the degree to which smoking-induced changes in response bias correlated with nicotine dependence on the FTND and smoking urges on the QSU.

Results

Sample

Sample characteristics are shown in [table 1](#). Half of the sample were African American ($n = 93$, 50.5%),

Table 1. Demographic, Clinical and Smoking Characteristics of the Entire Sample and Medication Subgroups

	D2 antagonism + (n = 71)		D2 antagonism - (n = 27)		Group Comparisons
<i>Demographics</i>					
Age, M (SD)	45.0	(10.8)	47.4	(9.1)	$t = 1.04, P = .30$
Years of education, M (SD)	11.9	(2.1)	12.2	(2.7)	$t = 0.58, P = .56$
Male, N (%)	50	(70.4)	13	(48.1)	$\chi^2 = 0.43, P = .04$
Race					$\chi^2 = 3.03, P = .39$
White, N (%)	21	(29.6)	10	(37.0)	—
Black, N (%)	34	(47.9)	14	(51.9)	—
Other, N (%)	16	(22.5)	3	(11.1)	—
Hispanic, N (%)	15	(21.1)	0	(0.0)	$\chi^2 = 6.74, P = .01$
Employed, N (%)	8	(11.3)	2	(7.4)	$\chi^2 = 1.63, P = .80$
<i>Clinical characteristics</i>					
Hosp., M (SD)	13.4	(18.6)	9.2	(7.4)	$t = 1.15, P = .25$
BPRS Total, M (SD)	39.6	(11.3)	43.2	(12.2)	$t = 1.36, P = .18$
BPRS Pos Sx, M (SD)	11.6	(5.0)	13.1	(5.1)	$t = 1.31, P = .19$
BPRS Neg Sx, M (SD)	9.5	(3.7)	9.6	(3.3)	$t = 0.04, P = .97$
BPRS Agit Sx, M (SD)	8.3	(2.7)	9.3	(4.0)	$t = 1.40, P = .17$
BPRS Dep Sx, M (SD)	10.2	(4.7)	11.3	(4.6)	$t = 0.97, P = .34$
<i>Smoking characteristics</i>					
Cigs./day, M (SD)	16.1	(13.4)	15.5	(17.3)	$t = 0.19, P = .85$
FTND Total, M (SD)	5.2	(2.0)	5.4	(2.0)	$t = 0.42, P = .67$
Baseline CO, M (SD)	28.4	(22.0)	30.2	(19.4)	$t = 0.37, P = .71$
Post-smoke CO, M (SD)	29.2	(20.4)	30.4	(19.0)	$t = 0.23, P = .82$
QSU Total, M (SD)	142.8	(33.0)	146.7	(48.4)	$t = 0.46, P = .65$

Note: M, Mean; SD, standard deviation, Hosp., hospitalizations; BPRS, Brief Psychiatric Rating Scale; Pos Sx, Positive Symptom subscale; Neg Sx, Negative Symptom subscale; Agit Sx, Agitation Symptom subscale; Dep Sx, Depressive Symptom subscale; FTND, Fagerstrom Test of Nicotine Dependence; CO, carbon monoxide; QSU, Questionnaire of Smoking Urges.

most were non-Hispanic, ($n = 158, 85.9\%$) and unemployed ($n = 166, 90.2\%$). The mean (\pm SEM) age was 45.73 ± 11.35 and range = 20–70, and the sample was two-thirds male ($n = 122, 66.3\%$). Symptoms were moderate (BPRS score = 41.32 ± 11.45 , mean lifetime hospitalizations = 11.65 ± 15.0). They reported smoking 15.57 ± 13.34 cigarettes/day in the past 3 months.

Of those who completed the PRT ($n = 174$), 114 (65.5%) had valid data both prior to and post-smoking. Those who were excluded (81.7% male; mean age = 46.7, SD = 12.8) did not differ from those who were retained in terms of symptom severity (BPRS) or nicotine dependence and craving (FTND and QSU; all P s > .20).

Smoking and Clinical Characteristics of Antipsychotic Medication Groups

Of those with valid PRT data, 98 could be classified as taking or not taking potent DA D₂ receptor antagonists (taking potent D₂ antagonists [D₂ antagonism+], $n = 71$; not taking potent D₂ antagonists [D₂ antagonism-], $n = 27$). Table 2 shows how the medication profiles were grouped. Independent samples t tests revealed no group differences in the average number of cigarettes smoked daily ($P = .85$), pre-assessment expired CO ($P = .71$), post-smoking expired CO ($P = .82$), self-reported nicotine dependence on the FTND ($P = .67$), craving on the QSU ($P = .65$), or symptom severity on the BPRS (total score and subscales,

all P s > .15). However, the groups did differ with respect to gender and ethnicity, where the D₂ antagonism + group contained a higher proportion of males, $\chi^2 = 0.43, P = .04$, and Hispanic individuals, $\chi^2 = 6.74, P = .01$.

Interactive Effects of Antipsychotic Type and Smoking on Reward Processing

A significant 3-way interaction emerged from the medication (D₂ antagonism+, D₂ antagonism-) \times smoking \times block ANOVA, $F(1,96) = 8.17, P = .005, \eta_p^2 = .08$ (figure 1). This interaction was followed up by considering all 2-way interactions, and Bonferroni-corrected post hoc tests of simple effects were conducted in cases where the 2-way interaction was significant. For brevity, only main effects and interactions involving smoking or medication are reported.

When examining the smoking \times block interaction separately within each medication group, we observed a significant smoking \times block interaction for the D₂ antagonism- group, $F(1,26) = 8.56, P = .007, \eta_p^2 = 0.25$, but not for the D₂ antagonism+ group ($P = .64$). In the D₂ antagonism- group, an increase in response bias from block 1 to block 2 of the task was observed following smoking ($P < .001$) but not prior to smoking ($P = .72$), indicating that smoking enhanced reward learning in this group.

When examining the medication \times block interaction separately for each smoking condition, at pre-smoking,

Table 2. Medication Profiles Classified as Having Potent DA D₂ Receptor Antagonism (D2 antagonism +) and Non-potent DA D₂ Receptor Antagonism (D2 Antagonism -)

Medication	D2 antagonism + (n = 71)	D2 antagonism - (n = 27)	n per Subcategory
Aripiprazole		X	11
Aripiprazole + quetiapine		X	1
Chlorpromazine	X		2
Chlorpromazine + quetiapine	X		1
Clozapine		X	7
Clozapine + haloperidol	X		1
Clozapine + risperidone	X		1
Fluphenazine	X		12
Haloperidol	X		13
Haloperidol + risperidone	X		1
Olanzapine	X		12
Paliperidone	X		14
Quetiapine		X	8
Risperidone	X		14
Risperidone + aripiprazole	X		1
Risperidone + olanzapine	X		1
Ziprasidone	X		2

Note: “X” shows how the different medication profiles (left-most column) within the sample were grouped.

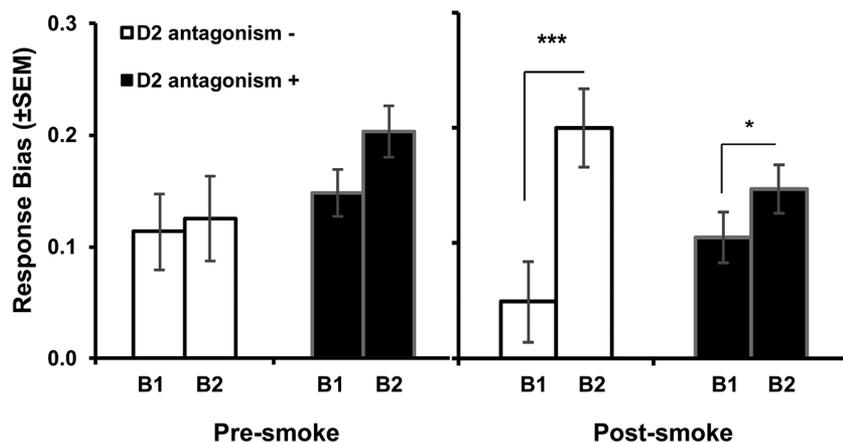


Fig. 1. Response bias in block 1 (B1) and block 2 (B2), prior to smoking and post-smoking, for the D₂ antagonism+ and D₂ antagonism- groups. Bars show mean (±SEM). **P* < .05; ****P* < .001.

the *medication* × *block* interaction was not significant (*P* = .28) nor was there a main effect of *medication* (*P* = .14). For the post-smoking condition, however, a significant *medication* × *block* interaction emerged, *F*(1,96) = 9.07, *P* = .003, η_p^2 = 0.09. Specifically, response bias increased from block 1 to block 2 in both the D₂ antagonism- (block 1 = 0.05, block 2 = 0.20, *P* < .001) and the D₂ antagonism+ group (block 1 = 0.11, block 2 = 0.15, *P* = 0.03); however, this increase was greater in the D₂ antagonism- group.

Figure 2 summarizes the interactive effects of medication and smoking on reward learning, conceptualized as the increase in response bias from block 1 to block 2. The increase in response bias was greater in the D₂ antagonism- group, indicating greater reward learning in these patients.

Independent samples *t* tests confirmed that the D₂ antagonism+ and the D₂ antagonism- groups did not differ significantly in terms of the ratio of rich to lean rewards that they received (summed across blocks) at pre- or post-smoking (both *P*s > 0.10), indicating that effects were not due to differential rates of exposure to the asymmetrical reinforcement schedule.

Because the 2 medication groups differed in terms of gender and ethnic makeup, further analyses were conducted to examine these variables as potential confounds. To maximize statistical power, we performed 2 *medication* × *smoking* ANCOVAs containing reward learning as the dependent variable and *gender/ethnicity* as the covariate. For the model containing *gender* as a covariate, a *medication* × *smoking* interaction emerged, *F*(1,95) = 7.23, *P* = .008, η_p^2 = 0.07. Bonferroni-corrected post hoc tests

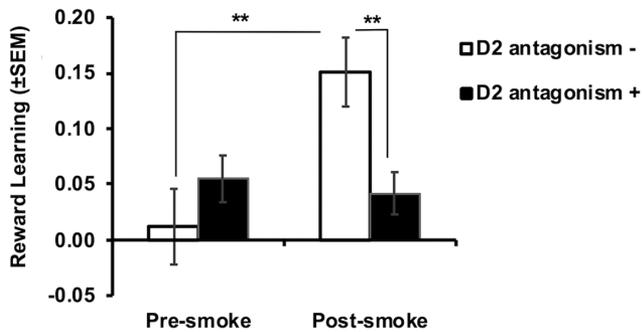


Fig. 2. Interactive effects of potent D₂ antagonist and smoking on reward learning (defined as response bias in block 2 – response bias in block 1). Bars show mean (±SEM). ** $P < .01$.

showed that after controlling for *gender*, reward learning increased from pre- to post-smoking in the D₂ antagonist– group ($P = .004$), but not in the D₂ antagonist+ group ($P = .69$). Furthermore, in this model, the main effect of *gender* was not significant, $F(1,95) = 0.06$, $P = .80$, $\eta_p^2 = 0.001$, nor was the *gender* × *smoking* interaction, $F(1,95) = 0.01$, $P = .64$, $\eta_p^2 = 0.002$. For the model containing *ethnicity* as a covariate, the *medication* × *smoking* interaction emerged, $F(1,95) = 8.29$, $P = .005$, $\eta_p^2 = 0.08$. Post hoc tests showed that after controlling for *ethnicity*, reward learning increased from pre- to post-smoking in the D₂ antagonist– group ($P = .006$), but not in the D₂ antagonist+ group ($P = .19$). Similarly, the main effect of *ethnicity* was not significant in this model, $F(1,95) = 1.11$, $P = .30$, $\eta_p^2 = 0.01$, and *ethnicity* did not interact with *smoking*, $F(1,95) = 0.25$, $P = .62$, $\eta_p^2 = 0.003$. These results suggest that differences in the gender and ethnic makeup of the medication groups did not drive our primary findings.

Effects of Potent D₂ Antagonists and Smoking on Discriminability

Mean discriminability at block 1 and block 2, pre- and post-smoking, across the 2 medication groups is shown in [supplementary figure S1](#). No main effects or interactions involving *medication* or *smoking* emerged from the *medication* × *smoking* × *block* ANOVA on discriminability scores (all P s > .10). This indicates that our primary findings were specific to reward processing, and not due to the effect of D₂ antagonists or smoking on more general task performance.

Associations Between Smoking-Related Increases in Reward Processing and Smoking Severity

Reward learning was not correlated with scores on the FTND or QSU (both P s > .05).

Discussion

The use of potent DA D₂ receptor antagonists has been linked to increased smoking and difficulty quitting in

smokers with schizophrenia.^{24–26} The aim of our study was to evaluate a putative mechanism for these effects by examining whether taking potent DA D₂ receptor antagonists was associated with a reduction in nicotine’s ability to enhance reward learning. Consistent with predictions, smoking increased reward learning, but only in individuals who were not taking potent DA D₂ antagonists. This effect was specific to reward learning, as effects were not observed on a measure of general task performance (ie, discriminability). Effects were also not attributable to demographic or clinical differences between the medication groups, or differences in nicotine dependence (FTND scores, expired CO, cigarettes per day), urges to smoke (QSU scores), or to post-smoking breath CO readings. Taken together, these findings point to a potential mechanistic explanation for increased smoking in individuals with schizophrenia who are treated with potent DA D₂ receptor antagonists. Specifically, these antagonists appear to diminish the effects of tobacco smoking on reward processing. Although not directly assessed in this study, we suggest that this may be a factor that drives compensatory increases in smoking behavior in order to achieve the same level of reward/stimulation.

Our findings align with prior work linking greater tobacco smoking in patients with schizophrenia to the use of first-generation antipsychotics,⁵² and research showing reductions in dependence and craving severity in individuals prescribed second-generation antipsychotics, such as aripiprazole and clozapine.^{26,29} Although we are the first to show that increased smoking in those treated with potent DA D₂ receptor antagonists may be related to a blunting of nicotine’s effects on reward processing, our interpretation is consistent with findings from an earlier study, which examined links between antipsychotic-related DA D₂ receptor occupancy and smoking in schizophrenia. Specifically, in patients who were randomized to olanzapine or risperidone, de Hann and colleagues⁵³ found that striatal D₂ receptor occupancy following antipsychotic treatment (stable dose for at least 6 weeks) was associated with future smoking, where greater D₂ receptor blockade predicted greater smoking frequency in the following 3 years. Recent studies suggest that nicotine may enhance associative conditioning.^{54,55} Therefore, a possible alternative explanation for our findings is that rather than blocking the effects of nicotine on reward sensitivity, potent DA D₂ receptor antagonists may diminish nicotine’s ability to facilitate the formation of an association between the rich stimulus and reward receipt. This, and other studies linking use of typical antipsychotics to blunted striatal activation in response to monetary reward cues,⁵⁶ supports the notion that potent DA D₂ receptor antagonists induce changes in the brain reward pathways, which may confer increased risk for nicotine dependence in individuals with schizophrenia.

Our initial hypothesis was based around evidence pointing to increased smoking in schizophrenia patients taking potent DA D₂ receptor antagonists;^{4,5} however, the 2 medication groups did not differ in smoking urges, dependence, or average number of cigarettes smoked per day. This may be because medication grouping occurred on a naturalistic basis, which meant that many participants were receiving several medications. It is possible that the polypharmacological profile of our sample may have reduced the magnitude of group differences in overt smoking behavior by comparison to other studies that have, for example, compared the effects of haloperidol monotherapy to no medication.²⁴ Additionally, other measures of smoking behavior may be more sensitive to group differences in nicotine dependence. For example, although de Haan and colleagues⁵³ found a relationship between antipsychotic-induced DA D₂ receptor occupancy and future smoking, they failed to find an association between D₂ receptor occupancy and smoking frequency at the time of scanning. As such, longitudinal measures of smoking may be more sensitive to medication-related differences in smoking behavior.

Our findings have important clinical implications for treating individuals with schizophrenia and co-occurring nicotine dependence. All patients with schizophrenia should be advised to quit and offered pharmacologic assistance with quitting. If a patient is unable to quit with evidence-based cessation treatment and is taking a potent DA D₂ receptor antagonist, switching to a different antipsychotic with lower affinity DA D₂ antagonism (eg, clozapine) or partial DA D₂ agonism (eg, aripiprazole) may be appropriate prior to a second trial of evidence-based cessation treatment. This recommendation aligns with recent findings suggesting that clozapine may be an effective treatment for comorbid schizophrenia and nicotine dependence.⁵⁷ In addition, when considering the use of a potent DA D₂ receptor antagonist for a patient with schizophrenia who smokes, it may be beneficial to implement concurrent efforts aimed at minimizing increases in smoking behavior.

Some limitations must be kept in mind when interpreting our findings. In our study, medication groupings were naturalistic rather than randomly assigned. Although the groups did not differ in terms of major demographic, clinical, or smoking characteristics, future research is needed to determine whether the blunted effect of smoking on reward processing observed in the D₂ antagonism+ group is specifically caused by potent DA D₂ receptor antagonism. It is possible that separate factors may cause a weaker effect of smoking on reward processing in certain individuals who are also more likely to be prescribed potent DA D₂ receptor antagonists. Future studies could also use direct administration of nicotine, rather than tobacco smoking, to ensure that effects are not confounded by ingestion of other substances in tobacco. Furthermore, in the pre-smoking condition, participants were tested after a 60-minute period of smoking abstinence. Because

this corresponds approximately with the half-life of nicotine (1–2 hours), it is possible that the baseline response bias would have been influenced by some residual levels of nicotine. Additional studies should incorporate a longer abstinence period, while avoiding withdrawal, which worsens reward function.⁵⁸ Finally, we did not examine smoking-induced changes in response bias in a non-psychiatric control sample. Future studies using a comparison sample are needed to determine whether the effects of smoking on response bias in patients not taking potent DA D₂ receptor antagonists is normative or blunted in comparison with control smokers.

In sum, our findings indicate that the use of potent DA D₂ receptor antagonists may reduce the ability of tobacco smoking to enhance reward-related processes in smokers with schizophrenia. Future longitudinal research is needed to examine the role of specific antipsychotic pharmacotherapies in the pharmacological management of schizophrenia and co-occurring tobacco smoking.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Funding

National Cancer Institute (R01CA168778).

Conflict of Interest

The funding body had no role in the preparation of this manuscript, interpretation of the findings, or the decision to publish this research. These findings were previously presented as a poster at the 73rd Annual Meeting of the Society of Biological Psychiatry in New York, May 10–12, 2018. Over the past 3 years, Dr Green has received funding for research studies from Novartis and Alkermes; he has served on a Data Safety Board for Eli Lilly, and he has served as an (unpaid) consultant to Otsuka and Alkermes. He is the coinventor of a patent, as well as a patent application, regarding development of a treatment of substance abuse. Over the past 3 years, Dr Brunette received funding from Alkermes to conduct research on medication treatment for co-occurring schizophrenia and alcohol use disorder. Drs Green and Brunette's interests were reviewed and are managed by the Geisel School of Medicine at Dartmouth in accordance with their conflict of interest policies. Over the past 3 years, Dr Pizzagalli received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Posit Science, and Takeda for activities unrelated to this study. Dr Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr Pizzagalli's interests were reviewed and are

managed by McLean Hospital and Partners HealthCare in accordance with their conflict of interest policies. Drs. Whitton, Roth, and Williams report no biomedical financial interests or potential conflicts of interest. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors.

References

- Dickerson F, Schroeder J, Katsafanas E, et al. Cigarette smoking by patients with serious mental illness, 1999-2016: an increasing disparity. *Psychiatr Serv*. 2018;69:147–153.
- Krishnadas R, Jauhar S, Telfer S, Shivashankar S, McCreedy RG. Nicotine dependence and illness severity in schizophrenia. *Br J Psychiatry*. 2012;201:306–312.
- Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry*. 2015;72:1172–1181.
- George TP, Vessicchio JC, Termine A, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry*. 2002;52:53–61.
- George TP, Ziedonis DM, Feingold A, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry*. 2000;157:1835–1842.
- Markou A. Review. Neurobiology of nicotine dependence. *Philos Trans R Soc Lond B Biol Sci*. 2008;363:3159–3168.
- Balfour DJ. The neurobiology of tobacco dependence: a pre-clinical perspective on the role of the dopamine projections to the nucleus accumbens. *Nicotine Tob Res*. 2004;6:899–912.
- Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. *Pharmacol Biochem Behav*. 2001;70:439–446.
- Laviolette SR, van der Kooy D. The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. *Nat Rev Neurosci*. 2004;5:55–65.
- Brody AL, Olmstead RE, London ED, et al. Smoking-induced ventral striatum dopamine release. *Am J Psychiatry*. 2004;161:1211–1218.
- Olausson P, Jentsch JD, Taylor JR. Repeated nicotine exposure enhances reward-related learning in the rat. *Neuropsychopharmacology*. 2003;28:1264–1271.
- Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE. A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. *Biol Psychiatry*. 2008;63:1061–1065.
- Moran LV, Stoeckel LE, Wang K, et al. Nicotine increases activation to anticipatory valence cues in anterior insula and striatum. *Nicotine Tob Res*. 2018;20:851–858.
- Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. *Nature*. 1998;393:76–79.
- Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry*. 2015;28:7–12.
- Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A. Pathway-specific dopamine abnormalities in schizophrenia. *Biol Psychiatry*. 2017;81:31–42.
- Khokhar JY, Dwiel LL, Henricks AM, Doucette WT, Green AI. The link between schizophrenia and substance use disorder: a unifying hypothesis. *Schizophr Res*. 2018;194:78–85.
- Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. *Nat Neurosci*. 2013;16:966–973.
- Ahnallen CG, Liverant GI, Gregor KL, et al. The relationship between reward-based learning and nicotine dependence in smokers with schizophrenia. *Psychiatry Res*. 2012;196:9–14.
- Klanker M, Sandberg T, Joosten R, Willuhn I, Feenstra M, Denys D. Phasic dopamine release induced by positive feedback predicts individual differences in reversal learning. *Neurobiol Learn Mem*. 2015;125:135–145.
- Jackson A, Silk S, Buhidma Y, Shoaib M. Varenicline, the clinically effective smoking cessation agent, restores probabilistic response reversal performance during withdrawal from nicotine. *Addict Biol*. 2017;22:1316–1328.
- Evins AE, Cather C, Pratt SA, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA*. 2014;311:145–154.
- Dutra SJ, Stoeckel LE, Carlini SV, Pizzagalli DA, Evins AE. Varenicline as a smoking cessation aid in schizophrenia: effects on smoking behavior and reward sensitivity. *Psychopharmacology (Berl)*. 2012;219:25–34.
- McEvoy JP, Freudenreich O, Levin ED, Rose JE. Haloperidol increases smoking in patients with schizophrenia. *Psychopharmacology*. 1995;119:124–126.
- Combs DR, Advokat C. Antipsychotic medication and smoking prevalence in acutely hospitalized patients with chronic schizophrenia. *Schizophr Res*. 2000;46:129–137.
- Kim SH, Han DH, Joo SY, Min KJ. The effect of dopamine partial agonists on the nicotine dependency in patients with schizophrenia. *Hum Psychopharmacol*. 2010;25:187–190.
- Dawe S, Gerada C, Russell MA, Gray JA. Nicotine intake in smokers increases following a single dose of haloperidol. *Psychopharmacology (Berl)*. 1995;117:110–115.
- Caskey NH, Jarvik ME, Wirshing WC, et al. Modulating tobacco smoking rates by dopaminergic stimulation and blockade. *Nicotine Tob Res*. 2002;4:259–266.
- George TP, Sernyak MJ, Ziedonis DM, Woods SW. Effects of clozapine on smoking in chronic schizophrenic outpatients. *J Clin Psychiatry*. 1995;56:344–346.
- Nordström AL, Farde L, Nyberg S, Karlsson P, Halldin C, Sedvall G. D₁, D₂, and 5-HT₂ receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. *Am J Psychiatry*. 1995;152:1444–1449.
- Casey DE. Drug evaluations: drug evaluation central & peripheral nervous systems: 'seroquel' (quetiapine): preclinical and clinical findings of a new atypical antipsychotic. *Expert Opin Investig Drugs*. 1996;5:939–957.
- Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biol Psychiatry*. 2005;57:319–327.
- Vrieze E, Ceccarini J, Pizzagalli DA, et al. Measuring extrastriatal dopamine release during a reward learning task. *Hum Brain Mapp*. 2013;34:575–586.
- Kaiser RH, Treadway MT, Wooten DW, et al. Frontostriatal and dopamine markers of individual differences in reinforcement learning: a multi-modal investigation. *Cereb Cortex*. 2017;28:4281–4290.
- Peechatka AL, Whitton AE, Farmer SL, Pizzagalli DA, Janes AC. Cigarette craving is associated with blunted reward processing in nicotine-dependent smokers. *Drug Alcohol Depend*. 2015;155:202–207.

36. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
37. Lukoff D, Nuechterlein K, Ventura J. Manual for the expanded brief psychiatric rating scale. *Schizophrenia Bull.* 1986;12:594–602.
38. Newman-Tancredi A, Kleven MS. Comparative pharmacology of antipsychotics possessing combined dopamine D2 and serotonin 5-HT1A receptor properties. *Psychopharmacology (Berl)*. 2011;216:451–473.
39. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: a new hypothesis. *Am J Psychiatry*. 2001;158:360–369.
40. Björkholm C, Jardemark K, Marcus MM, et al. Role of concomitant inhibition of the norepinephrine transporter for the antipsychotic effect of quetiapine. *Eur Neuropsychopharmacol.* 2013;23:709–720.
41. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology*. 2003;28:1400–1411.
42. Kegeles LS, Slifstein M, Frankle WG, et al. Dose-occupancy study of striatal and extrastriatal dopamine D2 receptors by aripiprazole in schizophrenia with PET and [18F]fallypride. *Neuropsychopharmacology*. 2008;33:3111–3125.
43. Natesan S, Reckless GE, Nobrega JN, Fletcher PJ, Kapur S. Dissociation between in vivo occupancy and functional antagonism of dopamine D2 receptors: comparing aripiprazole to other antipsychotics in animal models. *Neuropsychopharmacology*. 2006;31:1854–1863.
44. Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology*. 1999;20:612–627.
45. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström tolerance questionnaire. *Br J Addict.* 1991;86:1119–1127.
46. Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. *Br J Addict.* 1991;86:1467–1476.
47. Weinberger AH, Reutenauer EL, Allen TM, et al. Reliability of the Fagerström Test for Nicotine Dependence, Minnesota Nicotine Withdrawal Scale, and Tiffany Questionnaire for Smoking Urges in smokers with and without schizophrenia. *Drug Alcohol Depend.* 2007;86:278–282.
48. Javors MA, Hatch JP, Lamb RJ. Cut-off levels for breath carbon monoxide as a marker for cigarette smoking. *Addiction*. 2005;100:159–167.
49. Whitton AE, Kakani P, Foti D, et al. Blunted neural responses to reward in remitted major depression: a high-density event-related potential study. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1:87–95.
50. Macmillan N, Creelman C. *Detection Theory: A User's Guide*. United Kingdom: Cambridge University Press; 1991.
51. Hautus MJ. Corrections for extreme proportions and their biasing effects on estimated values of d' . *Behav Res Method Instrum Comput.* 1995;27:46–51.
52. Mallet J, Le Strat Y, Schürhoff F, et al. Tobacco smoking is associated with antipsychotic medication, physical aggressiveness, and alcohol use disorder in schizophrenia: results from the FACE-SZ national cohort. *Eur Arch Psychiatry Clin Neurosci.* 2018. doi:2010.1007/s00406-00018-00873-00407
53. de Haan L, Booij J, Lavalaye J, van Amelsvoort T, Linszen D. Occupancy of dopamine D2 receptors by antipsychotic drugs is related to nicotine addiction in young patients with schizophrenia. *Psychopharmacology (Berl)*. 2006;183:500–505.
54. Palmisano AN, Hudd EC, McQuade CM, de Wit H, Astur RS. The effects of nicotine on conditioning, extinction, and reinstatement in humans. *Addict Behav.* 2018;77:51–58.
55. Hahn B, Wells AK, Lenartowicz A, Yuille MB. Nicotine effects on associative learning in human non-smokers. *Neuropsychopharmacology*. 2018;43:2190–2196.
56. Schlagenhauf F, Juckel G, Koslowski M, et al. Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. *Psychopharmacology (Berl)*. 2008;196:673–684.
57. Mallet J, Le Strat Y, Schürhoff F, et al.; FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group. Cigarette smoking and schizophrenia: a specific clinical and therapeutic profile? Results from the FACE-schizophrenia cohort. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;79:332–339.
58. Pergadia ML, Der-Avakian A, D'Souza MS, et al. Association between nicotine withdrawal and reward responsiveness in humans and rats. *JAMA Psychiatry*. 2014;71:1238–1245.