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Brief Report

Depression Severity Moderates Reward Learning Among Smokers With Current or Past Major Depressive Disorder in a Smoking Cessation Randomized Clinical Trial

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Abstract

Introduction: Behavioral and pharmacological smoking cessation treatments are hypothesized to increase patients' reward learning to reduce craving. Identifying changes in reward learning processes that support effective tobacco-dependence interventions among smokers who experience depression may guide patients toward efficient treatment strategies. The objective was to investigate the extent to which adult daily cigarette smokers with current or past major depressive disorder (MDD) learned to seek reward during 12 weeks of treatment combining behavioral activation and varenicline. We hypothesized that a decline in reward learning would be attenuated (least to most) in the following order: (1) behavioral activation integrated with ST (BASC) + varenicline, (2) BASC + placebo, (3) standard behavioral cessation treatment (ST) + varenicline, (4) ST + placebo.

Methods: We ran a phase IV, placebo-controlled, randomized clinical trial with 300 participants receiving 12 weeks of one of four conditions across two urban medical centers. Depressive symptoms were measured using the Beck Depression Inventory-II (BDI). Reward learning was ascertained at weeks 1, 7, and 14 using the Probabilistic Reward Task (PRT), a laboratory task that uses an asymmetric reinforcement schedule to assess (a) learning to seek reward (response bias), (b) differentiate between stimuli, and (c) time to react to cues.

Results: There was a significant interaction of BDI group × PRT response bias. Response bias declined from weeks 7 to 14 among participants with high baseline depression symptoms. The other two BDI groups showed no change in response bias.

Conclusions: Controlling for baseline depression, participants showed a decrease in response bias from weeks 1 to 14, and from weeks 7 to 14. Treatment condition and abstinence status were unassociated with change in reward learning.

Implications: Smokers who report greater depression severity show a decline in reward learning despite their participation in smoking cessation treatments, suggesting that depressed populations pose unique challenges with standard smoking cessation approaches.

Trial Registration: ClinicalTrials.gov Identifier: NCT02378714.

Introduction

The low rate of smoking cessation among individuals who suffer from major depressive disorder (MDD) exerts a heavy burden on communities in the United States[1] and globally.[2] Although tobacco-dependence interventions offer health benefits, depressed patients disproportionately maintain their smoking use.[1] One clinical challenge is clarifying the extent to which depressed patients will respond to both pharmacotherapeutic (eg, varenicline, bupropion) and psychotherapy (eg, cognitive–behavioral mood management, standard behavioral therapy) modalities.[3] Current treatments for tobacco aim to help patients learn alternative rewarding methods that should compete with, and ultimately, reduce smoking. Reward learning is a psychological

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process through which a person learns to associate specific actions with positive or rewarding outcomes, thereby motivating the person to repeat behaviors that produce positive outcomes and avoid those that lead to negative ones. This associative process influences psychological health, such that abnormalities in reward learning can generate and perpetuate depression and its normalization can produce symptom relief. Thus, understanding how reward learning processes support smoking cessation interventions among smokers with current or past depression may improve outcomes for these patients and inform patient-treatment matching.[4] However, we have yet to investigate the extent to which reward learning processes change during tobacco-dependence interventions, and the extent to which such changes may be moderated by depression, particularly among smokers with MDD.

Alterations in reward learning have been implicated in the etiology, maintenance, and amelioration of both smoking and depression.[3] Specifically, reward learning is weaker among individuals with concurrent depression and tobacco dependence[5,6] among individuals experiencing nicotine withdrawal,[7] and among those with current and remitted depression.[8,9] Conversely, reward learning is enhanced by nicotine use,[3,10,11] prompting explanations that continued smoking during cessation treatment may signal a person's attempt to remediate reward learning deficits.[12] Yet, to date, no studies have investigated the change in reward learning during smoking cessation treatments with adults reporting current or past MDD.

Normalized reward mechanisms in psychotherapy appear to mediate recovery from depression.[13–15] For example, behavioral activation (BA), an evidence-based behavioral intervention derived from Cognitive–Behavioral Therapy, promotes reward and loss learning which predicts depression recovery[16] and smoking reduction.[17] Further, pharmacological treatments that target neurobiological substrates of reward may enhance reward learning. For example, varenicline, which is a partial agonist and partial blocker of the neuronal mechanisms that increase reward learning during smoking, is an effective treatment for smokers with current or past MDD.[18,19] Given the demonstrated impact of BA and varenicline on the reward system, investigation of reward learning within trials of both smoking cessation treatments is needed.

Behavioral and pharmacological smoking cessation treatments are hypothesized to increase patient hedonic experience and thus reduce craving, which mediates the effects of treatment on abstinence. This is based on the premise that aberrant performance of reward learning generates a functional problem that perpetuates excessive reward pursuit (eg, smoking) as has been found among adults with depression.[16] Thus, smoking is a method of maintaining a reward experience: Depending on the ability to transfer that experience to nonsmoking experiences while reducing nicotine use during treatment may predict the degree of treatment response.

Using data from a recently completed smoking cessation trial focusing on individuals with current and/or past MDD,[19] we hypothesized that a decline in reward learning would be attenuated in the following order: (1) behavioral activation integrated with ST (BASC) + varenicline, (2) BASC + placebo, (3) standard behavioral cessation treatment (ST) + varenicline, (4) ST + placebo. This is the first time, to our knowledge, that the effects of smoking cessation treatments were examined on reward learning over time, as well as whether alterations in reward learning were related to abstinence and depression severity.

Methods

We tracked the extent to which the ways in which adult daily cigarette smokers with current or past MDD learned to seek reward during 12 weeks of treatment combining BA and varenicline.[19] We conducted a phase IV, placebo-controlled, randomized clinical trial with 300 participants receiving 12 weeks of either behavioral activation integrated with ST (BASC) or standard behavioral treatment (ST) and either varenicline or placebo across two urban medical centers (Northwestern University, University of Pennsylvania). Conditions included (1) ST + placebo; (2) BASC + placebo; (3) ST + 1 mg/daily varenicline; or (4) BASC + 1mg daily varenicline. The primary outcome was carbon monoxide (CO) verified 7-day point prevalence abstinence at 24-week post-quit.

Demographics and smoking history were assessed, including nicotine dependence with the Fagerström Test for Cigarette Dependence (FTCD).[20,21] The daily number of cigarettes smoked since the last session was assessed with the timeline follow-back (TLFB) interview,[22] as was 7-day point prevalence abstinence, biochemically confirmed using a CO breath sample of ≤6 parts per million (ppm).[23] Psychiatric diagnoses were assessed using the Mini-International Neuropsychiatric Interview version 7.[24] Depression severity was evaluated with the Beck Depression Inventory (BDI-II).[25] Reward learning was ascertained at weeks 1, 7, and 14. The three subscales in the PRT, a computer task that uses an asymmetric reinforcement schedule[3,5,26] with E-Prime 2.0 (Psychological Software Tools). The subscales ascertain participants' ability to (a) learn to seek reward (response bias, RB); (b) discriminability (d') to differentiate the stimuli with the rich versus lean payoff; and (c) reaction time (RT, *ms*) reflecting general engagement. See Supplementary Materials for more details, including counterbalancing.

Descriptive statistics were used to summarize demographic and clinical variables. To test whether average RB differed over the course of treatment, we used a mixed-model analysis of variance (ANOVA) with mean RB, d', and RT at weeks 1, 7, and 14 as repeated measures, and Group (treatment condition) as the between-subjects factor. A similar mixed-model ANOVA was used to examine the effect of abstinence (between groups factor) on reward learning over the course of the trial. Where necessary, Huynh–Feldt correction was used.[27] We then conducted a repeated-measures ANOVA with RB at weeks 1, 7, and 14 and added depression symptom severity as measured by the BDI total score at Week 0 (baseline) as a covariate to test the interaction effects. Analyses were performed using SPSS statistical software version 19.0 (SPSS Inc., Chicago, IL).

Results

Of the 300 participants who enrolled in the parent study, 170 (56.7%) completed the study and 87 (30%) provided PRT data. Of the 87 participants who had complete, valid PRT data, 31 (35.6%) achieved 7-day point prevalence abstinence at the end of treatment (ie, week 24), while 18 (20.7%) achieved abstinence at week 27. The sample was 48.4 ± 12.5 years of age on average, and over half

were women (47/87, 54%). Most participants identified as White (49.4%), while 37.9% were Black/African American; 10.2% were either Asian, American Indian/Alaska Native, or multiracial; and 5.7% Hispanic. Less than half were never married (46%), while 27.5% were married or living as married, and 26.4% were divorced, separated, or widowed. Most of the sample completed high school (20.7%) or college (75.8%). Over half were employed (51.7%) and 48.3% were unemployed or retired. Smokers started smoking cigarettes at age 17.5 years on average (standard deviation [SD] = 4.5) and had smoked for 29.1 years on average (SD = 14.7). Participants smoked an average of 14 (SD = 6) cigarettes per day. Though 10.3% of smokers had current MDD only, 34.5% reported both current + past MDD, and 55.2% reported past MDD only. Baseline BDI-II severity was not associated with antidepressant medication at intake (p = .24; see Table S1).

The mixed-model ANOVAs evidenced no significant differences in RB as a function of treatment group (Table 1) or abstinence at week 14. Thus, we analyzed the full sample to examine hypothesized changes in RB during smoking cessation treatment. We conducted a repeated-measures ANOVA with RB at all three time points. The data violated the assumption of sphericity (Mauchly's $W(2) = .84$, $p = .001$) and therefore, the Huynh–Feldt correction was applied to the F test ($\epsilon = 0.88$). We observed from the corrected F test that there was a significant difference in RB across time points (F (1.75, 150.58) = 3.70, $p = .032$, partial $\eta 2 = 0.04$). Using tests of within-subjects contrasts (difference), we observed a significant difference in mean RB between week 7 ($M = 0.13$, SE = 0.01) and week 14 ($M = 0.10$, SE = 0.02; $F(1, 86) = 5.44$, $p = .022$, partial $\eta 2 = 0.06$), but not between week 1 ($M = .17$, SE = 0.02) and week 7 (F (1, 86) = 2.05, $p = .156$, partial $\eta 2 = 0.02$). With tests of within-subjects contrasts (simple), we observed a significant difference in mean RB between week 1 ($M = 0.13$, SE = 0.01) and week 14 ($M = 0.10$, SE = 0.02; F (1, 86) = 5.53, $p = .021$, partial $\eta 2 = 0.02$).

The mixed-model ANOVAs evidenced no significant differences in d' as a function of treatment group or as a function of abstinence (Table 1). Thus, we analyzed the full sample with a repeated-measures ANOVA with d' at all three time points to examine changes over the course of treatment, and no significant differences were found (F (2, 172) = 2.77, $p = .065$, partial $\eta 2 = 0.03$). The mixed-model ANOVAs evidenced no significant differences in average RT as a function of treatment group or as a function of abstinence (Table 1). Again, we analyzed the full sample with a repeated-measures ANOVA with RT at all three time points to examine changes during treatment, and no significant differences emerged (F (2, 172) = 1.80, $p = .169$, partial $\eta 2 = 0.02$).

Next, we conducted a repeated-measures ANOVA with RB at weeks 1, 7, and 14 and BDI at week 0 as a covariate to test the interactions. The data violated the assumption of sphericity (Mauchly's $W(2) = 0.84$, $p = .001$) and, therefore, the Huynh–Feldt correction was applied to the F test ($\epsilon = 0.89$). We observed from the corrected F test a significant interaction between RB and depression symptoms (F (1.78, 151.52) = 3.41, $p = .041$, partial $\eta 2 = 0.04$). Specifically, tests of within-subjects contrasts (difference) indicated that the interaction (RB × depression symptoms) was significant at week 7 versus week 14 ($F(1, 85) = 6.23$, $p = .015$, partial $\eta 2 = 0.07$), but not week 1 versus week 7 (F (1, 85) = 0.89, $p = .349$, partial $\eta 2 = 0.01$). Additionally, tests of within-subjects contrasts (simple) indicated that the interaction was significant at week 14 versus week 1 (F (1, 85) = 5.09, $p = .027$, partial $\eta 2 = 0.06$).

To interpret the interaction effect, we computed a variable that assigned participants to three classes based on BDI total scores: ≥1 SD above the mean ($n = 15$), ≤1 SD below the mean ($n = 18$), and within ±1 SD of the mean ($n = 54$; see Figure 1). Visual data inspection revealed that mean RB declined only among individuals with high levels of baseline depression symptoms.

Finally, to ensure that clinical variables were not confounding the association between reward learning and depression, we explored potential relationships between variables using the SPSS heterogeneous correlations extension, which automatically accounts for measurement levels to calculate Pearson product–moment correlations between

Table 1. PRT Performance Scores Across Treatment by Treatment Condition

Variables	ST + placebo, $N = 22$	BASC + placebo, $N = 13$	ST + varenicline, $N = 27$	BASC + varenicline, $N = 25$	Total sample, $N = 87$
	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)
Response bias					
Week 1	0.19 (0.03)	0.13 (0.04)	0.17 (0.03)	0.16 (.03)	0.16 (0.02)
Week 7	0.12 (0.03)	0.17 (0.03)	0.11 (0.02)	0.14 (.03)	0.14 (0.01)
Week 14	0.06 (0.04)	0.12 (0.05)	0.10 (0.03)	0.14 (0.03)	0.10 (0.02)
Discriminability					
Week 1	0.31 (0.04)	0.33 (0.05)	0.31 (0.04)	0.34 (0.04)	0.32 (0.02)
Week 7	0.35 (0.04)	0.36 (0.05)	0.35 (0.04)	0.38 (0.04)	0.36 (0.02)
Week 14	0.34 (0.04)	0.31 (0.05)	0.32 (0.04)	0.40 (0.04)	0.34 (0.02)
Reaction time (ms)					
Week 1	629.65 (26.04)	657.78 (33.88)	617.70 (23.51)	647.61 (24.43)	638.19 (13.64)
Week 7	652.92 (24.76)	637.03 (32.20)	610.22 (22.35)	624.29 (23.22)	631.12 (12.96)
Week 14	828.05 (24.37)	647.58 (31.70)	605.01 (22.00)	613.58 (22.86)	623.55 (12.76)

BASC = Behavioral Activation Integrated with Standard Behavioral Cessation Treatment; M = Mean; SE = standard error; ST = Standard Behavioral Cessation Treatment. Lower response bias values reflect lower reward responsiveness. Same for discriminability and reaction time values.

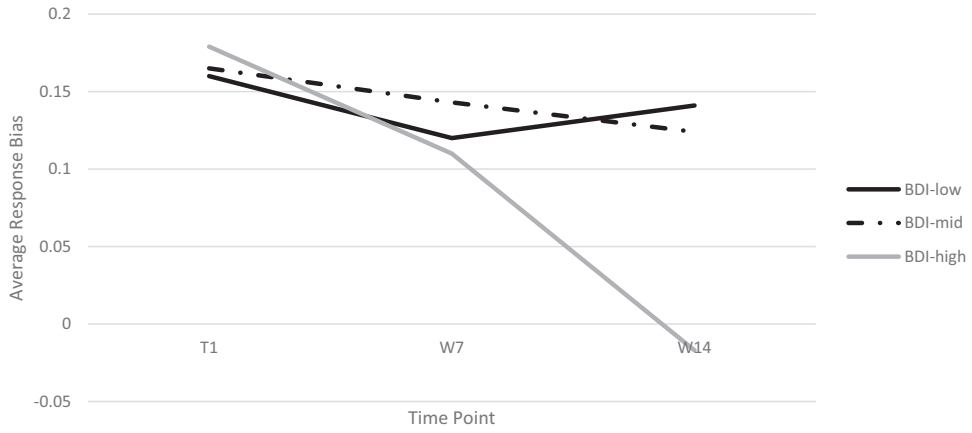

Figure 1. Interaction between response bias (RB) and BDI classification. Classifications determined from BDI-II total scores: low (≤1 SD below the mean), mid (within ± 1 SD of the mean), high (≥1 SD above the mean). Lower RB values reflect lower reward responsiveness. Same for discriminability and reaction time values. BDI = Beck Depression Inventory; SD = standard deviation.

scale variables, polyserial correlations between scale and categorical variables, and polychoric correlations between categorical variables. Specifically, the matrix correlated PRT variables (eg, RB, discriminability, RT, percent change) with tobacco use measures (eg, cigarette use, FTCD score, time to first cigarette, menthol cigarette use), and clinical measures (eg, scores on BDI, BAI, antidepressant medication use, lifetime non-MDD diagnoses, and regular alcohol use; Table S2).

Discussion

We observed novel findings that high depressive symptom severity at baseline was associated with a greater decline of reward learning for smokers with current or past MDD, particularly during the latter half of treatment. These findings are consistent with prior studies supporting baseline depressive severity as a moderating influence on reward learning during antidepressant interventions.[28,29] Contrary to hypotheses, no significant differences were found for change in mean reward learning across treatment groups, which included ST and BASC with and without varenicline, and as a function of abstinence status at the end of 12 weeks of treatment.

This is the first study to investigate differences in reward learning among smokers with past or current MDD undergoing smoking cessation treatment, building on prior work showing attenuated smoking with varenicline.[30,31] Studies have shown a link between reward learning deficits and depression,[3,5,6] core depressive symptoms of anhedonia,[32,33] executive function,[34] and working memory,[35,36] suggesting that depression attenuates reward learning. The current study critically extends this literature, detecting a greater decline of reward learning when depression severity is higher among individuals who participate in standard psychotherapy and pharmacotherapy smoking cessation programs.

Smokers with elevated depression who underwent treatment for smoking cessation may have shown declines in their reward learning due to anhedonia and negative affect. Depression involves a reduced ability to experience pleasure along with motivational challenges, making it harder to experience reward and make the decision to refrain from smoking. Depression is linked with a reduced responsiveness to reward experiences as well as positive reinforcement.[37,38] Further, negative affect, including sadness, irritability, and anxiety may have drained the rewarding experience of quitting smoking and reduced the perception of reward. As depression is a complex disease with interconnected factors, more work is needed to understand when and how smokers with elevated depression can stay motivated and rewarded through treatment.[16,39]

In this study, we observed modest outcomes with smoking cessation approaches that focus on single cognitive targets. This applies to BASC, which aimed to increase access to rewarding cues and reinforce nonsmoking activities,[40] as well as with varenicline, which blocks nicotinic activation of α4β2 receptors thwarting its ability to stimulate the central nervous mesolimbic dopamine system, as well as treatments that aim to reduce negative affect.[41] Findings from the current study support the goal of activating reward learning among adults with MDD[17] as an important treatment target during smoking cessation. Such treatment approaches may offer therapeutic options for more severely depressed smokers.

The main limitation of interpretability is that many participants did not contribute valid PRT data (leaving treatment early or offering invalid administrations), suggesting that our findings are preliminary and require replication. Other limitations include the use of correlational methods that preclude causal interpretations, our use of strict eligibility criteria that may constrain generalizability, and though we included the treatment condition in our analyses, we offer this as a brief report with preliminary results that require replication. Future studies should utilize larger samples and alternate analytic approaches as well as different types of assessments (eg, use of neuroimaging using learning behavioral tasks) to better characterize the nature of reward system changes during smoking cessation treatment among individuals with depression. Computational models may also delineate the precise mechanism of change in reward learning.

Overall, our findings support the use of repeated PRT assessments among smokers who endorse current or past MDD in a smoking cessation treatment study. New initiatives to build treatment programs that discern for whom reward-based treatments are useful would be worthwhile. Also, new research on multi-model targets may enhance nonsmoking reward experience for depressed adult smokers.

Supplementary Material

Supplementary material is available at *Nicotine and Tobacco Research* online.

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The funder (NIH/National Cancer Institute) had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. Pfizer, which donated active varenicline and matching placebo, also had no role in any aspect of the study including manuscript preparation or submission approval.

Declaration of Interests

JKG has received royalties from American Psychological Association. BH, PhD, has served on scientific advisory boards for Pfizer and received medication and placebo free of charge from Pfizer for the current study. RAS, PhD, has received varenicline and placebo free of charge from Pfizer for National Institutes of Health-funded trials and has served as a consultant for Pfizer, GlaxoSmithKline, and PalliaTech. Over the past 3 years, DAP has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, Dana Foundation, Wellcome Leap, Millennium Pharmaceuticals, and NIMH; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software; he has a financial interest in Neumora Therapeutics, which has licensed the copyright to the human version of the probabilistic reward task through Harvard University. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors have no conflicts of interest or relevant disclosures.

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Author Contributions

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Data Availability Statement

Data available on request.

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