Received: 2 August 2022 | Accepted: 28 March 2023

DOI: 10.1111/add.16209

RESEARCH REPORT

ADDICTION SSA

Efficacy and safety of combination behavioral activation for smoking cessation and varenicline for treating tobacco dependence among individuals with current or past major depressive disorder: A 2 × 2 factorial, randomized, placebo-controlled trial

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Abstract

Background and Aims: Treatment of depression-related psychological factors related to smoking behavior may improve rates of cessation among adults with major depressive disorder (MDD). This study measured the efficacy and safety of 12 weeks of behavioral activation for smoking cessation (BASC), varenicline and their combination.

Design, Setting, Participants: This study used a randomized, placebo-controlled, 2 × 2 factorial design comparing BASC versus standard behavioral treatment (ST) and varenicline versus placebo, taking place in research clinics at two urban universities in the United States. Participants comprised 300 hundred adult smokers with current or past MDD.

Interventions: BASC integrated behavioral activation therapy and ST to increase engagement in rewarding activities by reducing avoidance, withdrawal and inactivity associated with depression. ST was based on the 2008 PHS Clinical Practice Guideline. Both treatments consisted of eight 45-min sessions delivered between weeks 1 and 12. Varenicline and placebo were administered for 12 weeks between weeks 2 and 14.

Measurements: Primary outcomes were bioverified intent-to-treat (ITT) 7-day point-prevalence abstinence at 27 weeks and adverse events (AEs).

Findings: No significant interaction was detected between behavioral treatment and pharmacotherapy at 27 weeks ($\chi^2_{(1)} = 0.19$, $P = 0.67$). BASC and ST did not differ ($\chi^2_{(1)} = 0.43$, $P = 0.51$). Significant differences in ITT abstinence rates ($\chi^2_{(1)} = 4.84$, $P = 0.03$) emerged among pharmacotherapy arms (16.2% for varenicline, 7.5% for placebo), with results favoring varenicline over placebo (rate ratio = 2.16, 95% confidence

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Funding information
Feinberg School of Medicine; National Cancer Institute, Grant/Award Numbers: R01 CA184211, R01 CA197332; National Center for Advancing Translational Sciences, Grant/Award Number: UL1 TR001422; Robert H. Lurie Comprehensive Cancer Center

interval = 1.08, 4.30). All significant differences in AE rates after start of medication were higher for placebo than varenicline.

Conclusion: A randomized trial in smokers with major depressive disorder found that varenicline improved smoking abstinence versus placebo at 27 weeks without elevating rates of adverse events. Behavioral activation for smoking cessation did not outperform standard behavioral treatment, with or without adjunctive varenicline therapy.

KEYWORDS
adults, behavioral activation therapy, major depressive disorder, smoking cessation treatment, tobacco dependence, varenicline

INTRODUCTION

There have been many calls for greater attention to the treatment of tobacco dependence in individuals with major depressive disorder (MDD) [1–6]. MDD is the most common mental health disorder world-wide [7], with a prevalence that increased during the COVID-19 pandemic [8]. Although the prevalence of smoking appears to have declined among people with MDD [9], more than 30% of individuals with depression are daily smokers [9–11]. Smokers with depression are more likely to smoke heavily, perceive smoking as more pleasurable than other traditionally rewarding activities, show greater dependence and experience more severe withdrawal than smokers without MDD [12–15]. Psychological processes impaired among individuals with MDD, namely reward experience and cognition, are linked with smoking relapse [16–18].

Little is known about strategies that optimize tobacco treatments for smokers with MDD because nearly all clinical trials have excluded this group [19–21]. Only five trials have focused upon smokers with MDD [22–26]. Two of these were limited by sample sizes of fewer than 50 participants [24, 26]. In the only trial of varenicline for this group [23], varenicline improved abstinence at 52 weeks (28.5%) versus placebo (17.5%). Cessation rates with varenicline are higher in smokers without mental health disorders [27], suggesting the need for novel behavioral interventions to optimize treatment.

A behavioral treatment that may improve smoking cessation for individuals with MDD is behavioral activation (BA). There has been only one study of BA for smoking cessation in depression-vulnerable individuals. In a pilot study involving 68 smokers with elevated depressive symptoms [Beck Depression Inventory (BDI)-II scores ≥ 10], but no current MDD, BA added to standard behavioral treatment (ST) and nicotine patch improved abstinence at 26 weeks (14.3%) versus ST and nicotine patch (0%) [28]. Treatment combining BA and varenicline may address core psychological barriers to cessation for individuals with MDD. Varenicline attenuates smoking reward, craving and withdrawal [18, 29–34] and reduces withdrawal-related cognitive impairment [18]. BA decreases avoidance coping and increases reward experience [35–37]. Attenuation of smoking reward by varenicline could enhance the effect of BA on increasing reward experience, further reducing smoking reward.

Concern about the safety of varenicline led to a boxed warning in 2008. Since that time, studies have supported the safety of varenicline in smokers with and without mental health disorders [27], resulting in the removal of the warning in 2016. Unlike smokers without mental health disorders, those with mental health disorders, including MDD, are less likely to be prescribed varenicline than nicotine replacement therapy [38], despite the greater effectiveness of varenicline [27, 38]. Lingering concerns about the safety of varenicline among smokers with mental health disorders continue to limit it use.

Treatment combining BA and varenicline has not been evaluated, but may promote abstinence for individuals with MDD. In this study, we evaluated the efficacy and safety of this novel treatment combination in a 2 × 2 randomized, placebo-controlled design. Enrollment was opened to people with past MDD, because this group also is at heightened risk for diminished treatment outcome [20], and prior trials targeting people with current MDD expanded reach to people with past MDD only [23]. We hypothesized that behavioral activation for smoking cessation (BASC) would increase long-term abstinence versus ST and that varenicline would increase long-term abstinence versus placebo. In addition, we evaluated on an exploratory basis the hypothesis that a combination of BASC and varenicline would maximize abstinence. Finally, we hypothesized that varenicline and placebo would not differ in adverse event (AE) rates at the end of treatment (EOT).

METHODS

Study design

In this randomized, placebo-controlled trial, individuals with current and/or past MDD received 12 weeks of either BASC or ST and either varenicline or placebo (NCT02378714). Recruitment and treatment

follow-up were conducted between 06/01/2015 and 03/13/2020. Treatment follow-up occurred at week 27, approximately 13 weeks after treatment was discontinued.

Setting

The study was conducted in research clinics at Northwestern University (Chicago, IL, USA) and the University of Pennsylvania (Philadelphia, PA, USA). The study was approved by the Institutional Review Boards of both universities and overseen by a Data and Safety Monitoring Board.

Participants

Eligible participants were 300 adults who smoked daily (≥ 1 cigarettes/day), had a life-time diagnosis of MDD, without psychotic features, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [39] and were interested in quitting smoking. People reporting any level of daily smoking were included, given the US population data showing a substantial reduction in consumption among people who continue to smoke cigarettes daily [40]. Additional inclusion criteria and the complete list of exclusion criteria are described in the Supporting information.

Procedure

Initial eligibility screening was completed by telephone. Final eligibility screening, informed consent, treatment randomization and the baseline assessment was completed at the intake session (week 0). Computer-based randomization was stratified on clinical site, sex and level of depressive symptoms (minimal/mild versus moderate/severe) using the BDI-II [41]. Permuted blocks of fixed size with unequal allocation ratio across arms were used to maximize the number of participants assigned to varenicline arms. After clicking a randomization button within the password-protected section of the study database, the database assigned the behavioral treatment arm and blister pack kit number for either a varenicline or placebo blister pack. The appropriate blister pack was produced by the Investigational Drug Service at Northwestern. While counselors were necessarily aware of behavioral treatment assignment, all members of the research team were blind to medication assignment. The appropriate behavioral treatment binder was prepared by the assigned counselor. The treatment binder and first 2 weeks of medication were given to the participant at their first behavioral treatment session. Medication blister packs for weeks 3–7 were dispensed at week 3 and week 7 for weeks 8–13. Treatment was discontinued at week 14. Assessments were conducted at weeks 0, 1, 3, 4, 6, 7, 8, 10, 12, 14 and 27. Abstinence was assessed at the week 27 follow-up. Participants who reported not smoking in the past 7 days were asked to attend an in-person visit for breath carbon monoxide (CO) confirmation using Vitalograph® breath monitors. Outcome assessors were blind to behavioral and pharmacological treatment assignment. Participants received up to $140.00 for completing assessments and up to $60.00 for travel.

Interventions

Behavioral treatment

BASC and ST interventions were manualized and equated on contact time. Both intensive treatments consisted of eight 45-minute sessions between weeks 1 and 12, occurring weekly for the first 4 weeks and every other week for the last 8 weeks. Except for sessions 1 and 3 [target quit date (TQD)], treatment was delivered by telephone. Participants submitted their completed between-session assignments to study therapists using web-based forms, by e-mail/fax or by telephone.

Behavioral activation for smoking cessation

BASC integrated behavioral activation therapy [36, 42, 43] with standard behavioral treatment and addressed smoking as a behavior that prevents and restricts opportunities for healthy rewarding behaviors. A key emphasis was on reducing environmental and perceived stress and lost reward due to smoking cessation and on identifying and establishing social environmental changes that promote abstinence. Two pre-quit sessions introduced participants to: (1) self-monitoring of mood and behavior; (2) assessment of personal values to refine the treatment plan; and (3) scheduling of substitute rewarding activities aligned with their abstinence goal. At the TQD session (session 3 at week 3), participant experiences with initial abstinence were reviewed and functional analysis of behavior was introduced. Information obtained was used to generate a plan to increase rewarding activities and relationships, reduce avoidant responses to distressing experiences and facilitate implementation of smoking trigger management. Sessions 4–8 incorporated strategies to address avoidance patterns, especially those involving smoking, and replace them with adaptive behaviors. Strategies included managing stress pile-up using step-by-step task deconstruction, recognizing rumination [44] as avoidance coping, becoming more proactive and less mood-dependent, short-term goal setting and long-term goal planning to increase pleasure and mastery aligned with personal life goals.

Standard behavioral treatment

ST was based on the 2008 US Public Health Service clinical practice guideline [45] and on the behavioral treatment used in our previous trials [46, 47]. Treatment components included self-monitoring, identifying smoking triggers and alternative trigger management strategies, relaxation, social support for non-smoking and relapse prevention.

Pharmacotherapy

Varenicline and placebo medication were administered for 12 weeks between weeks 2 and 14 according to US Food and Drug Administration-approved labeling: days 1–3 (0.5 mg once daily), days 4–7 (0.5 mg twice daily) and days 8–84 (1.0 mg twice daily).

Behavioral treatment fidelity

The BASC and ST protocols were distinguished starting with therapist training workshops and audio-recorded mock therapy sessions designed to establish therapist proficiency. Therapists conducted both BASC and ST sessions and used condition-specific session checklists to guide session content. All sessions were audio-recorded. Therapist competence, adherence and treatment contamination were rated using a counseling adherence and competence rating scale that was developed for the study. The integrated BASC/ST fidelity assessment, unlike condition-specific assessments of treatment fidelity, allowed the raters to verify scheduled content and detect contamination by the alternate treatment. The assessment enabled simple scoring for therapist competence, adherence and contamination.

Recordings from early, middle and late treatment sessions were randomly selected and scored independently by investigators (J.K.G. and A.H.) for therapist competence in delivering treatment, adherence to the treatment model and cross-condition of treatment methods. Therapists attended weekly supervision by videoconference for review of recorded sessions, treatment principles and techniques, participant between-session assignments and treatment plans. Therapist retraining was triggered by a session adherence rating less than 90% or any evidence of cross-condition contamination. Fifteen therapists delivered the two behavioral treatments.

Measures

Primary outcomes

Pre-specified primary outcomes were 7-day point-prevalence abstinence at 27 weeks, confirmed by CO breath levels ≤ 6 parts per million [48] and AEs, including serious adverse events (SAEs), between varenicline and placebo arms.

Secondary outcomes

Pre-specified secondary outcomes were CO-verified 7-day point-prevalence abstinence at week 14 and time to continuous and prolonged abstinence failure at weeks 14 and 27. Continuous abstinence was defined as self-reported no smoking between the TQD and the follow-up visit. Prolonged abstinence was defined in a similar manner, but allowed for a 2-week grace period past the TQD [49, 50].

Other measures

Demographic, smoking history and medical/psychiatric history were assessed at week 0. The Fagerstrom Test of Cigarette Dependence was used to assess tobacco dependence [51, 52]. Motivation to quit smoking was assessed using the readiness ladder [53, 54]. DSM-5 disorders were assessed with the mini-international neuropsychiatric interview (MINI) version 7.0.0 [55]. Depressive symptoms were measured at all time-points except week 2, using the BDI-II [41]. Medication side effects were measured using a 28-item checklist rating scale at week 1, weeks 3–14 and week 27. An established algorithm was used to classify a side effect report as an AE or SAE [47, 56]. Suicide risk was assessed at all time-points using the side effect checklist and the Columbia suicidality severity rating scale (C-SSRS) [57]. Any report of suicidal ideation/behavior was classified as a SAE. Blood pressure was assessed at weeks 0, 1, 3, 7, 14 and 27. Medication adherence was assessed via collection of used blister packs and time-line follow-back assessment [58]. Adherence was defined as having taken the prescribed medication on at least 80% (67 of 84) of total days prescribed [47]. Counseling adherence was defined as completing at least 75% (six of eight) of treatment sessions.

Statistical analysis

Sample size calculations

BASC versus ST abstinence rate estimates were based on the MacPherson *et al.* [28] pilot randomized trial involving smokers with mildly elevated depressive symptoms. Varenicline versus placebo abstinence rate estimates were based on the Anthenelli *et al.* trial [23] involving smokers with current or past (≤ 2 years) MDD. In the MacPherson *et al.* trial, abstinence rates at 26 weeks were 14.3% for behavioral activation treatment and 0% for standard treatment. In the Anthenelli *et al.* trial, abstinence rates at 24 weeks were 31.3% for varenicline and 18.2% for placebo. A minimum of 75 participants was to be assigned to each behavioral treatment group receiving placebo, while a minimum of 90 participants was to be assigned to each behavioral treatment group receiving varenicline. Such a configuration (n = 330) would have guaranteed 81% power for testing the superiority of BASC versus ST (18 versus 5% abstinence) among the 150 participants receiving placebo and 97% power for testing the superiority of varenicline versus placebo (24 versus 5% abstinence) among the 180 participants receiving ST, at one-tailed alpha = 0.05.

Analytical plan

Analyses of abstinence rates were conducted using intent-to-treat (ITT) principles [59]. ITT estimates of 7-day point-prevalence abstinence rates at 14 and 27 weeks and the corresponding rate ratios

(RR) across treatment arms were obtained via modified Poisson Regression [60], which produces the same point estimates as ordinary Poisson regression, but corrects the resulting standard errors when the underlying data are binomially distributed. Given the factorial nature of the design and the potential of heterogeneous treatment effects across sites, we fitted a BASC × varenicline × site interaction model and simplified its terms in a hierarchical fashion, starting with the three-way interaction.

Time to continuous and prolonged abstinence failure were evaluated non-parametrically using Kaplan–Meier survival curves [61]. Between-arm differences at weeks 14 and 27 were assessed using a log-rank test [62, 63]. For the time to continuous and prolonged abstinence failure analyses, the TQD was used as the origin.

Differences between varenicline and placebo arms in AE and SAE rates at pre-quit 1, week 6 and week 14 were tested using Fisher's exact test. Holm's procedure [64] was used to control family-wise error below 5% at each time-point. Differences in uncontrolled hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg) rates and suicide risk were tested with logistic regression. *Post-hoc* analysis of differences in level of depression by treatment arm was conducted with Kruskal–Wallis analysis of variance (ANOVA), which can accommodate departures from normality.

Missing data

ITT findings are based on the full sample randomized at baseline and employ a missing-not-at-random (MNAR) assumption that missing = smoking [65]. We supplemented these by inverse probability of retention weighting (IPRW) [66] analyses with stabilized weights [67, 68], which reweigh the set of responders at each follow-up, so that it is representative of the sample at baseline. Baseline characteristics in Table 1 showing persistent imbalances between respondents and non-respondents after IPRW [69–71] (see Supporting information) were entered as covariates in the propensity-weighted logistic regression models estimated via the *Survey* package in R [72]. Such analyses produce consistent estimates of the logistic regression coefficients under a missing-at-random (MAR) assumption [65]. We also present responder-only analyses, also known as 'complete-case' analyses [73], that allow us to more clearly understand how IPRW corrects the observed abstinence rates for dropout bias.

RESULTS

Participants

Figure 1 presents the participant flow across the study. Socio-demographic, smoking and psychiatric characteristics of the sample are shown in Table 1. Only use of antidepressant medication and educational level differed significantly among treatment arms.

Integrity of the behavioral treatments

Overall therapist competence was rated as 'very good' [mean = 5.3, standard deviation (SD) = 1.0, n = 134 sessions] and overall participant understanding was rated as 'good' (mean = 4.6, SD = 1.2, n = 134 sessions). Overall competence ratings did not differ by therapist level of education (Bachelor's degree versus Master's degree) or treatment session number (Ps > 0.05). Competence in delivering the ST protocol was rated as 'very good' (mean = 5.9, SD = 0.5), whereas competence in delivering the BA treatment protocol was rated as 'good' (mean = 4.3, SD = 0.9). Therapist adherence to the ST protocol was 80.8% (SD = 23.5) and adherence to the BASC protocol was 71.7% (SD = 18.4). The mean level of adherence across the two treatment protocols (76.2%) indicated that most prescriptive strategies were presented as intended. Level of therapist adherence differed by treatment arm, favoring the ST protocol, during the early and middle treatment sessions (P < 0.001, P < 0.03, respectively), but not at week 12 (P > 0.05) which marked the end of behavioral treatment. Adherence did not differ by therapist education (P > 0.05). Regarding therapist cross-condition contamination, levels of proscribed strategies were low in both the BASC (6.6%) and ST arms (3.7%), with minimal contamination across arms (5.2%).

Behavioral treatment and medication adherence

Sixty-three per cent of participants overall were adherent to behavioral treatment and there were no differences among arms ($\chi^2_{(3)}$ = 7.23, P = 0.065). The mean number of behavioral treatment sessions completed was: 6.1 (SD = 2.2) for ST + placebo, 5.3 (SD = 2.6) for BASC + placebo, 6.3 (SD = 2.2) for ST + varenicline and 5.9 (SD = 2.3) for BASC + varenicline. Overall rate of medication adherence was 43.7%. Medication adherence rates by arm were: 51.5% for ST + placebo, 35.3% for BASC + placebo, 48.2% for ST + varenicline and 39.8% for BASC + varenicline. There was no overall difference in medication adherence rates among treatment arms ($\chi^2_{(3)}$ = 4.82, P = 0.185). The BASC × varenicline interaction was statistically non-significant for both behavioral treatment adherence (P = 0.29) and medication adherence (P = 0.90)

Treatment and study retention

As seen from Figure 1, overall retention of participants was 59.3% at 14 weeks (EOT) and 56.7% at 27 weeks (end of study). Borderline significant differences in retention rates among the treatment arms at 14 weeks ($\chi^2_{(3)}$ = 7.59, P = 0.055) appeared driven by a lower retention rate in the BASC + placebo arm: 63.2% for ST + placebo, 45.6% for BASC + placebo, 66.7% for ST + varenicline, and 61.7% for BASC + varenicline. Borderline significant differences in retention rates among treatment arms ($\chi^2_{(3)}$ = 7.54, P = 0.057) also emerged at 27 weeks: 57.4% for ST + placebo, 42.6% for BASC + placebo, 63.0% for ST + varenicline and 61.4% for BASC + varenicline.

TABLE 1 Participant characteristics by treatment arm and overall sample.

Characteristic	ST + placebo *n* = 68	BASC + placebo *n* = 68	ST + varenicline *n* = 81	BASC + varenicline *n* = 83	Overall sample *N* = 300
Demographic					
Age (years)	50.3 (10.8)	50.7 (13.5)	48.7 (12.7)	50.3 (13.2)	50.0 (12.6)
Sex (% female)	39 (57.4)	38 (55.9)	44 (54.3)	44 (53.0)	165 (55.0)
Race					
American Indian/Alaska Native	0	0	1 (1.2)	1 (1.2)	2 (0.7)
Asian	0	1 (1.5)	3 (3.7)	0	4 (1.3)
Black/African American	40 (58.8)	37 (54.4)	43 (53.1)	37 (44.6)	157 (52.3)
White	25 (36.8)	27 (39.7)	28 (34.6)	36 (43.4)	116 (38.7)
More than one race	1 (1.5)	3 (4.4)	4 (4.9)	8 (9.6)	16 (5.3)
Unknown or not reported	2 (2.9)	0	0	1 (1.2)	3 (1.0)
Refused	0	0	2 (2.5)	0	2 (0.7)
Ethnicity (% Hispanic/Latino)	4 (5.9)	5 (7.4)	5 (6.2)	4 (4.8)	18 (6.0)
Marital status					
Never married	28 (41.1)	26 (38.2)	38 (46.9)	37 (44.5)	129 (43.0)
Married	14 (20.6)	8 (11.7)	11 (13.5)	14 (16.8)	47 (15.6)
Divorced/separated	20 (29.4)	24 (35.3)	22 (27.1)	18 (21.7)	84 (28.0)
Widowed	1(1.5)	5 (7.4)	3 (3.7)	6 (7.2)	15 (5.0)
Living as married	5 (7.4)	5 (7.4)	6 (7.4)	7 (8.4)	23 (7.6)
Education*					
Grade school	0	1 (1.5)	0	0	1 (0.3)
Some high school	2 (2.9)	3 (4.4)	4 (5.0)	7 (8.4)	16 (5.3)
High school graduate or GED	11 (16.2)	23 (33.8)	27 (33.3)	15 (18.1)	76 (25.3)
Some college/technical school	38 (55.9)	22 (32.4)	24 (29.6)	32 (38.6)	116 (38.8)
College graduate	17 (25.0)	19 (27.9)	26 (32.1)	29 (34.9)	91 (30.3)
Income per year					
Less than $20 000	26 (38.2)	25 (36.8)	29 (35.8)	30 (36.1)	110 (36.7)
$20 000–35 000	14 (20.6)	16 (23.5)	21 (25.9)	17 (20.5)	68 (22.7)
$35 001–50 000	14 (20.6)	8 (11.8)	11 (13.6)	13 (15.7)	46 (15.3)
$50 001–75 000	8 (11.8)	12 (17.6)	6 (7.4)	12 (14.5)	38 (12.7)
More than $75 000	6 (8.8)	6 (8.8)	13 (16.1)	10 (12.2)	35 (11.7)
Employment					
Retired/unemployed	42 (61.8)	31 (45.6)	38 (46.9)	42 (50.6)	153 (51.0)
Part-time	11 (16.2)	18 (26.5)	15 (18.5)	16 (19.3)	60 (20.0)
Full-time	15 (22.0)	19 (27.9)	28 (34.6)	25 (30.1)	87 (29.0)
Smoking					
Cigarettes smoked per day	15.0 (7.2)	15.6 (9.1)	14.4 (6.6)	15.5 (8.5)	15.2 (7.9)
Duration of smoking (years)	32.0 (11.9)	31.9 (15.1)	28.8 (14.5)	32.5 (14.0)	31.2 (14.0)
FTCD	5.4 (2.1)	5.3 (2.0)	5.2 (2.1)	5.1 (2.3)	5.2 (2.1)
Readiness to quit	7.0 (1.3)	6.8 (1.4)	6.7 (1.1)	6.7 (1.2)	6.8 (1.2)
Time to first cigarette after waking					
5 minutes or less	35 (51.5)	32 (47.1)	38 (47.0)	33 (39.8)	138 (46.0)
More than 5 minutes	33 (48.5)	36 (52.9)	43 (53.0)	50 (60.2)	162 (54.0)
Cigarette type					
Menthol cigarettes only	43 (63.2)	40 (58.8)	47 (58.0)	48 (57.8)	178 (59.3)
Regular cigarettes (or both)	24 (35.3)	28 (41.2)	34 (42.0)	34 (41.0)	120 (40.0)

(Continues)

TABLE 1 (Continued)

Characteristic	ST + placebo *n* = 68	BASC + placebo *n* = 68	ST + varenicline *n* = 81	BASC + varenicline *n* = 83	Overall sample *N* = 300
Carbon monoxide level (p.p.m.)	12.4 (6.2)	12.2 (7.6)	12.7 (8.3)	13.3 (7.7)	12.7 (7.5)
Psychiatric					
Major depressive disorder status[a]					
Current and past MDD	27 (39.7)	28 (41.2)	32 (39.5)	32 (38.6)	119 (39.7)
Current MDD only	4 (5.9)	4 (5.9)	12 (14.8)	8 (9.6)	28 (9.3)
Past MDD only	37 (54.4)	36 (52.9)	37 (45.7)	43 (51.8)	153 (51.0)
Antidepressant medication* (% yes)	15 (22.1)	28 (41.2)	15 (18.5)	24 (28.9)	82 (27.3)
Other psychiatric diagnosis[b]	28 (41.2)	35 (51.5)	40 (49.4)	30 (36.1)	133 (44.3)
Depressive symptoms (BDI-II)	18.5 (10.8)	19.0 (12.3)	19.5 (12.2)	18.0 (10.8)	18.7 (11.5)
BDI-II classification					
Minimal	21 (30.9)	24 (35.3)	27 (33.3)	28 (33.7)	100 (33.3)
Mild	23 (33.8)	13 (19.1)	16 (19.8)	19 (22.9)	71 (23.7)
Moderate	13 (19.1)	17 (25.0)	20 (24.7)	25 (30.1)	75 (25.0)
Severe	11 (16.2)	14 (20.6)	18 (22.2)	11 (13.3)	54 (18.0)
Regular alcohol drinker (% yes)	35 (51.5)	41 (61.2)	48 (60.0)	36 (43.4)	160 (53.7)
Alcohol drinks in a typical week	5.9 (6.0)	6.2 (6.5)	6.3 (5.5)	7.8 (5.7)	6.5 (5.9)

Note: Values are *n* (%) or mean (standard deviation). Some percentages do not add to 100% due to missing data. With respect to cigarettes smoked per day, 10 participants (3.3%) reported smoking fewer than five cigarettes per day and 60 participants (20.0%) reported smoking fewer than 10 cigarettes daily. Beck Depression Inventory (BDI)-II interpretation: 0–13, minimal; 14–19, mild; 20–28, moderate; 29–63, severe.
Abbreviations: BASC, behavioral activation for smoking cessation; FTCD, Fagerstrom Test for Cigarette Dependence; ST, standard behavioral treatment; GED, general education development; MDD, major depressive disorder; p.p.m., parts per million.
[a]DSM-5 defined MDD without psychotic features;
[b]other DSM-5 disorder as classified using the Mini-International Neuropsychiatric Interview.
*$P < 0.05$.

These differences appeared driven by significantly lower retention rates for placebo versus varenicline (50.0 versus 62.2%) ($\chi^2_{(1)} = 4.50$, $P = 0.034$).

Primary outcomes

Treatment efficacy

Table 2 presents the 7-day point-prevalence abstinence rates by treatment arm at 14 and 27 weeks. ITT estimates are supplemented by responder-only analyses. Abstinence rates among study participants providing smoking data at each follow-up are shown: (1) without adjustment for non-response (also known as a 'complete-case analysis'); and (2) with IPRW adjustment for non-response and additional regression adjustment for baseline covariates showing imbalances (standardized mean difference > 0.20) even after propensity weighting.

Hierarchical hypothesis testing of the BASC × varenicline × site interaction model produced a simplified model for 14-week ITT abstinence rates with only a significant varenicline × site interaction term ($\chi^2_{(1)} = 4.98$, $P = 0.026$), which led us to analyze varenicline versus placebo effects separately by site. Merging across behavioral treatment arms, varenicline outperformed placebo in both sites, but the RR estimates were a lot stronger at UPenn than Northwestern (RR = 10.78 versus 1.91). As seen from Table 2, this was the result of much higher abstinence rates under placebo at Northwestern versus UPenn (15.5 versus 2.8%). In contrast, varenicline abstinence rates showed no cross-site variation between Northwestern and UPenn (30.0 versus 30.3%).

Responder-only analyses at 14 weeks produced larger abstinence rate estimates but slightly attenuated RRs at both UPenn and Northwestern (RR = 8.93 versus 1.75). Finally, IPRW combined with regression adjustment for baseline degree of tobacco dependence (the only imbalanced covariate showing associations with 14-week abstinence; $P < 0.001$) increased crude estimates of the abstinence rates in the placebo arms, leaving the varenicline arms largely unaffected. As a result, the varenicline versus placebo abstinence rate ratios were attenuated even further at both UPenn and Northwestern (RR = 5.93 versus 1.53).

Hierarchical hypothesis testing of the BASC × varenicline × site interaction model produced a simplified model for 27-week ITT abstinence rates with only a significant varenicline main effect ($\chi^2_{(1)} = 4.84$, $P = 0.028$). In particular, both varenicline and placebo 27-week rates in the overall sample were approximately halved compared relative to those observed at Northwestern at 14 weeks, dropping to 16.2 and 7.5% respectively (RR = 2.16). Responder-only and IPRW analyses again produced larger abstinence rate estimates, but their rate ratio

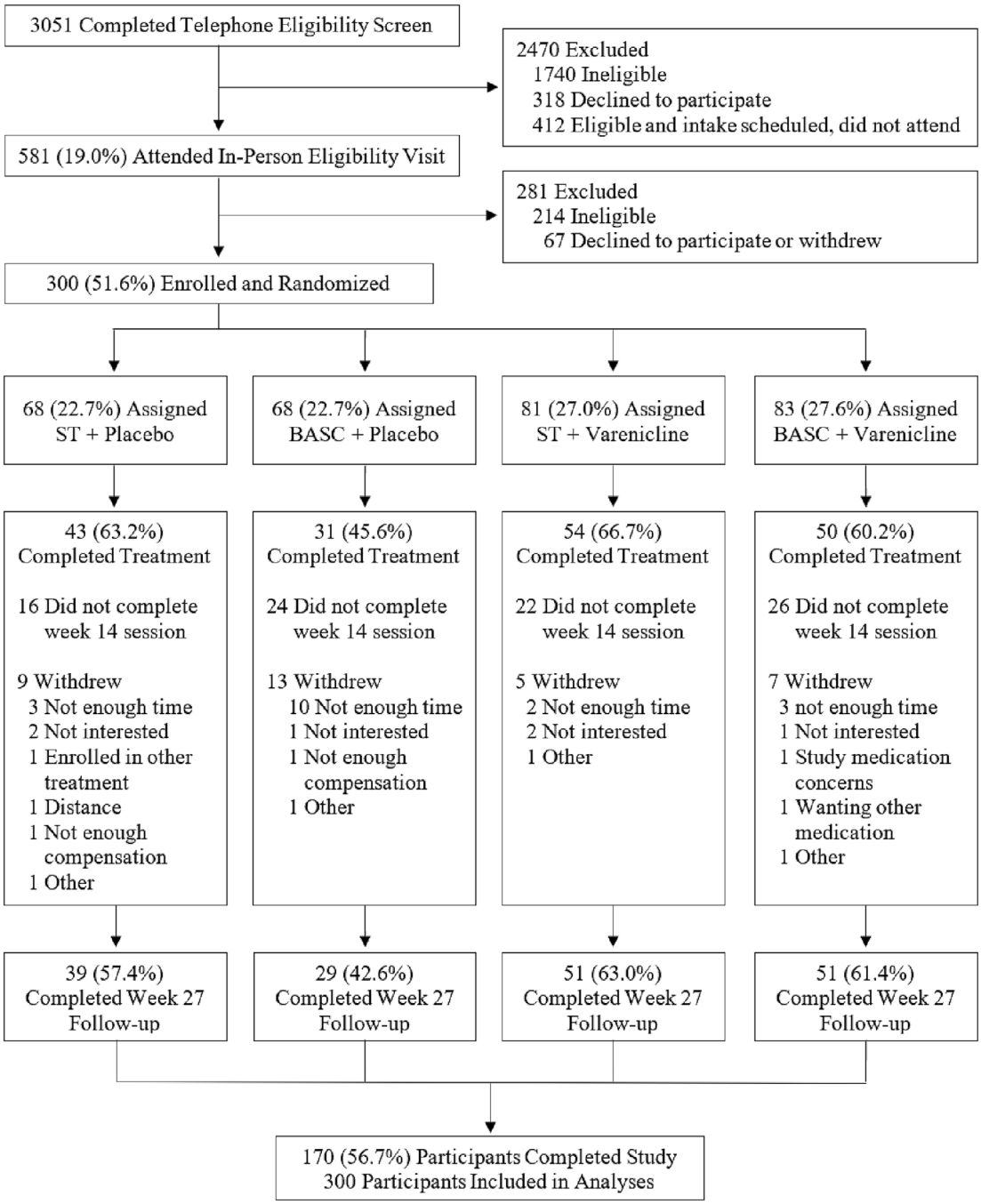

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. CONSORT flow diagram showing participant flow through the phases of enrollment, treatment allocation and completion, follow-up and study completion.

estimates (RR = 1.79 versus 2.10) remained close to the ITT estimate, suggesting an approximate doubling in the abstinence rates under varenicline compared to placebo.

Varenicline safety

AE rates by medication arm at weeks 1, 6 and 14 are shown in Figure 2. At week 1, which occurred 1 week before starting medication, there were no statistically significant differences between varenicline and placebo arms in AE rates. At week 6, AE rates differed between varenicline and placebo only for sleep problems ($P = 0.035$). At week 14, rates of dry mouth ($P = 0.009$) and anxiety ($P = 0.023$) differed significantly between varenicline and placebo arms. At weeks 6 and 14, all statistically significant AEs were higher for placebo than for varenicline. The total number of AEs by week of treatment and medication arm were the following: week 1 (572 for varenicline, 431 for placebo), week 6 (314 for varenicline, 251 for placebo) and

TABLE 2 Bioverified 7-day point-prevalence abstinence at 14 and 27 weeks.

	Varenicline	Placebo	Ratio	*p*-Value
14 weeks: Northwestern				
Intent-to-treat	30.0 (21.8, 41.1)	15.5 (9.2, 26.2)	1.93 (1.05, 3.56)	0.0345
Responder only	46.8 (34.3, 64.0)	26.8 (16.4, 43.8)	1.75 (0.98, 3.10)	0.0588
IPRW responder only	46.9 (35.3, 62.3)	30.6 (19.4, 48.3)	1.53 (0.91, 2.57)	0.1068
14 weeks: UPenn				
Intent-to-treat	30.3 (21.5, 42.9)	2.8 (0.7, 10.8)	10.78 (3.11, 37.40)	0.0001
Responder only	49.2 (36.3, 66.7)	5.5 (1.8, 16.4)	8.93 (2.88, 27.69)	0.0002
IPRW responder only	48.3 (36.0, 64.9)	8.1 (2.2, 29.8)	5.93 (1.57, 22.41)	0.0095
27 weeks				
Intent-to-treat	16.2 (11.3, 23.3)	7.5 (4.2, 13.5)	2.16 (1.08, 4.30)	0.0277
Responder only	26.2 (18.6, 36.8)	14.7 (8.4, 25.6)	1.79 (0.93, 3.43)	0.0820
IPRW responder only	27.8 (20.1, 38.4)	13.2 (6.7, 26.0)	2.10 (1.01, 4.40)	0.0498

Values represent abstinence percentages and 95% confidence intervals. Self-reported 7-day point-prevalence abstinence was confirmed with breath carbon monoxide (CO) levels ≤ 6 parts per million. IPRW = inverse probability of response weighting; BASC = behavioral activation for smoking cessation. All estimates were Fagerstrom Test for Cigarette Dependence-corrected. One participant had no CO value. BASC × varenicline × site interactions, BASC × varenicline interactions and BASC main effects were not significant at either time-point (*P*s > 0.05). Varenicline by site interactions and site main effects were only significant at 14 weeks ($P < 0.05$).

week 14 (190 for varenicline, 197 for placebo). Regarding blood pressure, there were no significant differences between medication arms in rates of hypertension across treatment (*P*s > 0.05). Both varenicline- and placebo-treated participants showed reductions in hypertension between baseline and week 14. The same pattern was observed for suicide risk between and within medication arms.

Only one SAE rate differed significantly between varenicline and placebo across the three time-points: suicidal ideation ($P = 0.032$), which was higher for varenicline than placebo at week 1 before medication was started (Figure 3). None of the nominally significant *P*-values survived multiplicity adjustment. The total number of SAEs by week and medication arm were the following: week 1 (56 for varenicline, 48 for placebo), week 6 (42 for varenicline, 44 for placebo) and week 14 (20 for varenicline, 17 for placebo). There were no suicides or suicide attempts during the study. Twenty-one participants overall reported 32 SAE cases that were classified as 'possibly related' to study medication. Of these, 11 participants were in the varenicline arm and 10 participants were in the placebo arm. The 11 varenicline-treated participants reported 19 (59.4%) of the 32 'possibly related' cases. A tabular summary of AE and SAE rates at weeks 1, 6 and 14 by medication arm is presented in Supporting information, Table S1.

Secondary outcomes

Continuous abstinence rates remained steady at 2.9% for ST + placebo and 1.8% for BASC + placebo between weeks 14 and 27, but declined further to 5.6% for ST + varenicline and 2.4% for BASC + varenicline during this period (Figure 4). Differences in time to prolonged abstinence failure were significant over 14 weeks ($\chi^2_{(3)} = 15.5$, $P = 0.001$) and remained highly significant over 27 weeks ($\chi^2_{(3)} = 11.1$, $P = 0.01$). Prolonged abstinence rates at week 14 were 6.8% for ST + placebo, 5.6% for BASC + placebo, 21.7% for ST + varenicline and 14.1% for BASC + varenicline. As shown in Figure 5, prolonged abstinence rates also remained steady at 6.8% for ST + placebo and 5.6% for BASC + placebo between weeks 14 and 27, but showed declines to 9.0% for ST + varenicline and 9.4% for BASC + varenicline during this period.

There were no statistically significant differences in depression levels among treatment arms at baseline or any of the follow-up time-points (*P*s > 0.05). As can be seen in Supporting information, Figure S1, all treatment arms showed a decline in depression levels among responders between weeks 1 and 14.

DISCUSSION

This is the first trial, to our knowledge, to evaluate the efficacy of BASC for individuals with MDD and the first to evaluate the efficacy of adding behavioral activation to varenicline. Consistent with limited prior research on individuals with MDD, varenicline improved both short- and long-term abstinence relative to placebo. Additionally, varenicline did not increase risk of adverse or serious adverse events, even among the large proportion of individuals in the sample with current, severe, untreated MDD. These data further increase confidence in the safety of varenicline for smokers with MDD.

A strength of our study is that our sample was racially and socioeconomically diverse and spanned varied psychiatric presentations: 49.0% of participants had current MDD, 44.3% had other DSM diagnoses (including substance use disorder), only 27.3% were being treated for depression, and 16% reported one or more past suicide

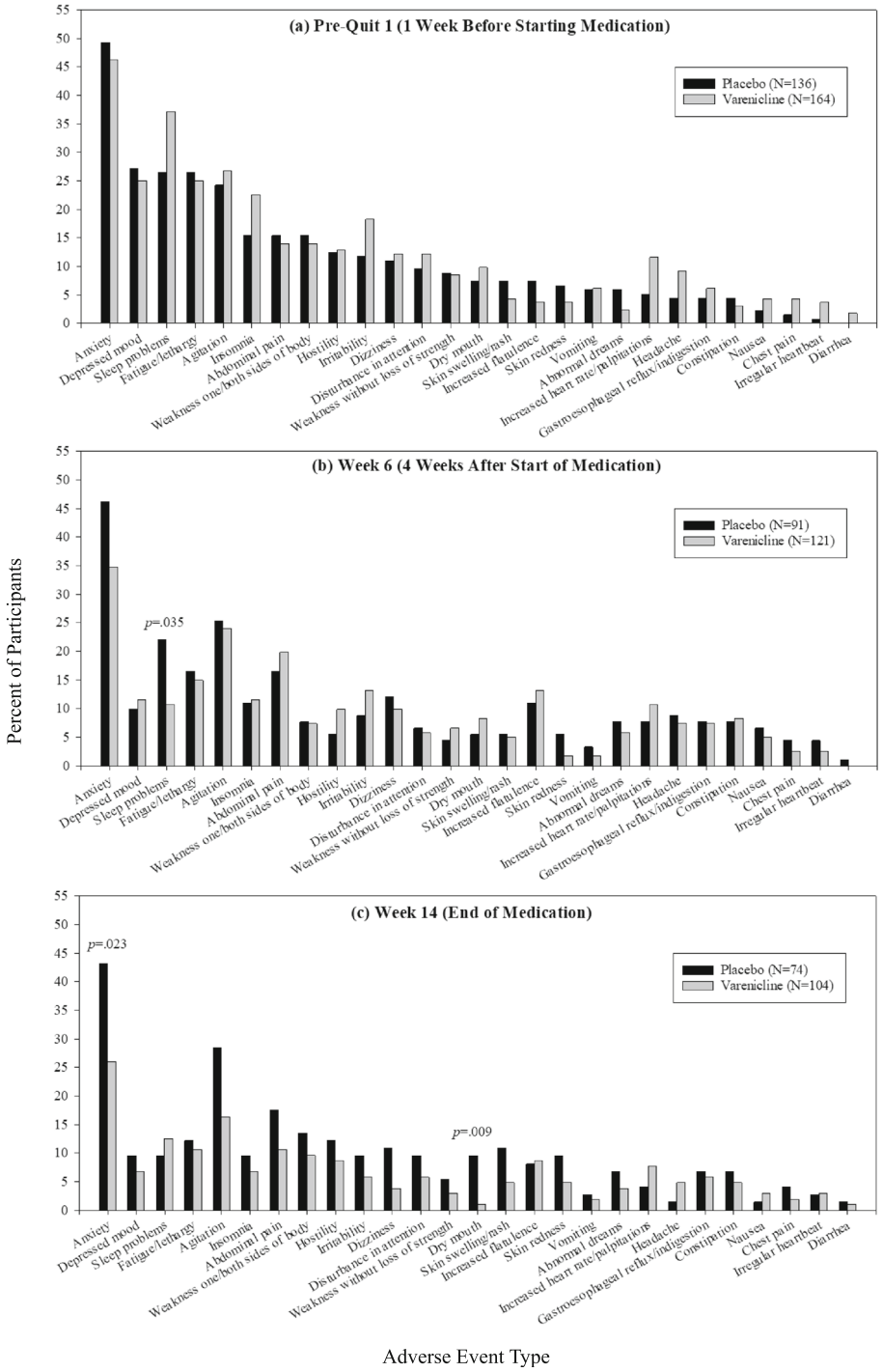

FIGURE 2 Adverse events by medication arm and assessment time-point. Adverse event rates for varenicline and placebo arms at pre-quit 1 session and at weeks 6 and 14. The pre-quit 1 session occurred 1 week before starting medication. Week 14 was the end of medication treatment. For panels (b) and (c), event type is ordered based on frequency at the pre-quit 1 session for placebo-treated participants.

attempts. There also was variability in motivation to quit [74]. Only 53.0% of participants endorsed planning to quit in the next 30 days. A limitation of our study was the low treatment adherence. Even though most treatment was delivered remotely by telephone, which increases utilization versus clinic-based treatment [75], adherence to behavioral treatment and medication was low, as was study retention overall, consistent with other trials focused upon individuals with depressive disorders [22, 23]. BASC alone had the lowest rates of adherence. Advancing treatment for smokers with MDD will require effective strategies for improving adherence to behavioral treatment and pharmacotherapy [76].

Abstinence rates were lower than those observed in Anthenelli and colleagues' trial, the only other trial of varenicline focused upon smokers with MDD [23]. In that trial, involving participants who were clinically stable, the ITT abstinence rates at week 24 were 31.3% for varenicline and 18.2% for placebo. The higher abstinence rates achieved in both the varenicline and placebo arms may be explained in part by the longer-term behavioral treatment added to the

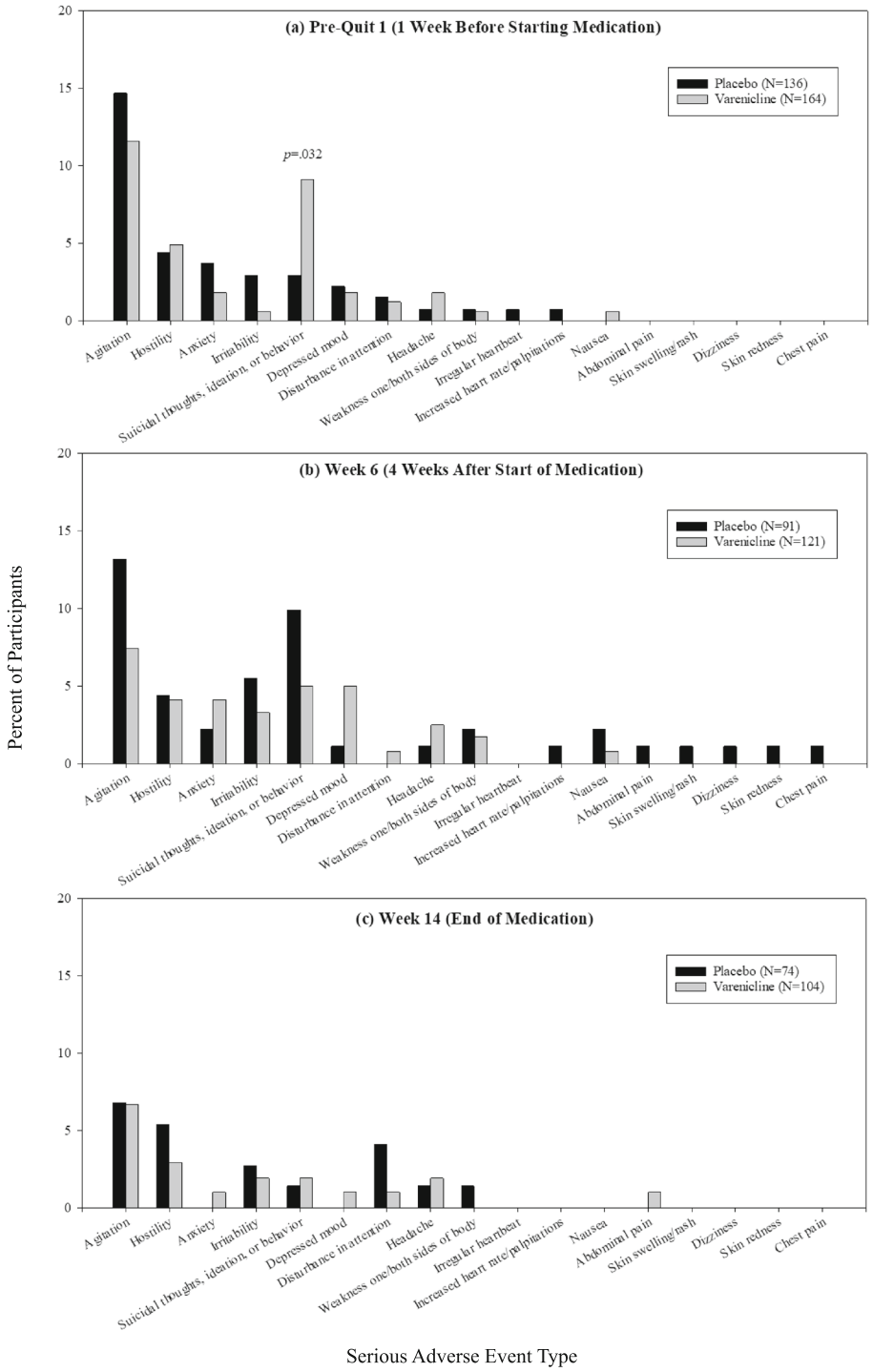

FIGURE 3 Serious adverse events by medication arm and assessment time-point. Serious adverse event rates for varenicline and placebo arms at pre-quit 1 session and at weeks 6 and 14. The pre-quit 1 session occurred 1 week before starting medication. Week 14 was the end of medication treatment. For panels (b) and (c), event type is ordered based on frequency at the pre-quit 1 session for placebo-treated participants.

pharmacotherapy in that study. All participants received 25 10-minute sessions of counseling to week 52. Extended-duration behavioral treatment (i.e. delivering treatment over a longer time-period), compared with standard treatment, increases the rate of abstinence among individuals without mental health disorders [77]. A more likely explanation for the lower abstinence rates in our study, however, is that our sample was more socio-economically disadvantaged and psychiatrically unstable. Socio-economic factors may also explain the difference between our two clinical sites in response to behavioral treatment alone (placebo arms), because a lower proportion of the participants treated at UPenn were currently employed, had achieved a college education or had an annual income greater than $20 000.

Our results for varenicline also are consistent with the secondary analysis of EAGLES trial data recently conducted by Cinciripini and colleagues [78]. Among the large cohort of participants with MDD (n = 2635), required to be clinically stable and without active substance use disorder, varenicline produced significantly higher continuous abstinence rates than bupropion, nicotine patch or placebo. The

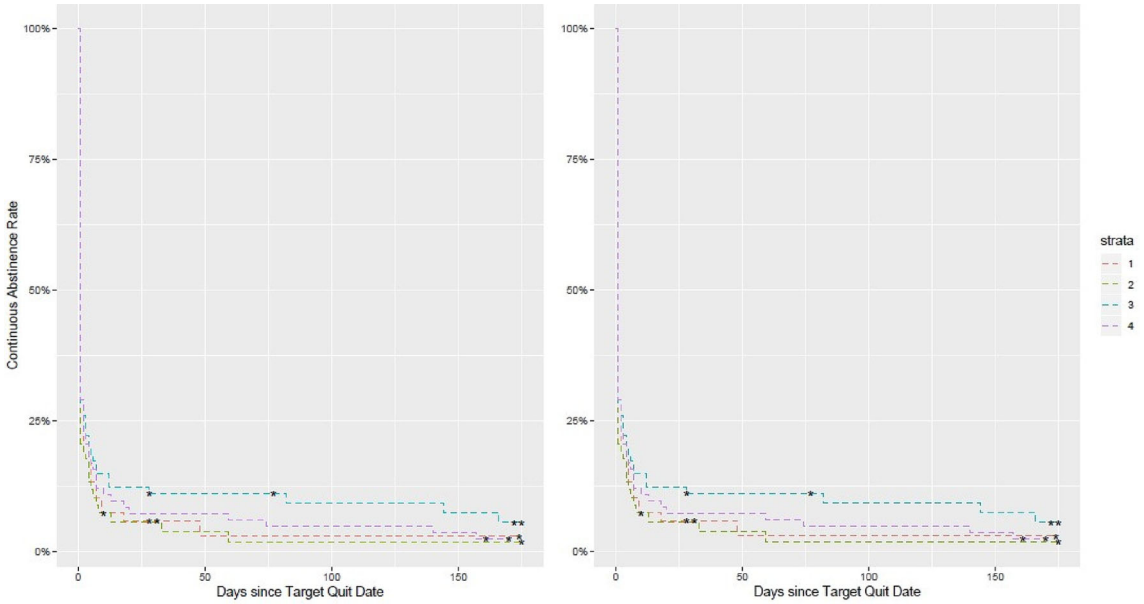

FIGURE 4 Time to continuous abstinence failure during the 14-week treatment phase (left panel) and 27-week study period (right panel). Time to continuous abstinence failure was evaluated non-parametrically using Kaplan–Meier survival curves. The week 3 session (target quit date) was used as the origin. Strata 1 = behavioral activation for smoking cessation (BASC) + placebo, Strata 2 = standard behavioral treatment (ST) + placebo, Strata 3 = ST + varenicline, Strata 4 = BASC + varenicline.

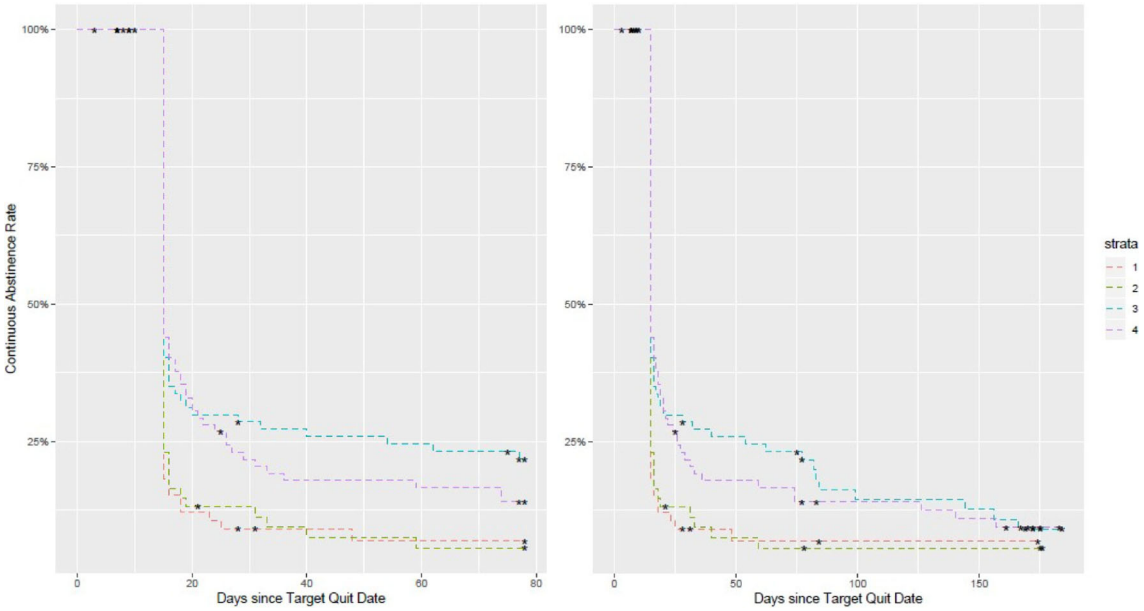

FIGURE 5 Time to prolonged abstinence failure after a 2-week grace period during the 14-week treatment phase (left panel) and 27-week study period (right panel). Time to prolonged abstinence failure after a 2-week grace period was evaluated nonparametrically using Kaplan–Meier survival curves. The week 3 session (target quit date) was used as the origin. Strata 1 = behavioral activation for smoking cessation (BASC) + placebo, Strata 2 = standard behavioral treatment (ST) + placebo, Strata 3 = ST + varenicline, Strata 4 = BASC+varenicline.

rate of neuropsychiatric adverse events was comparable across treatment arms. We agree with Cinciripini and colleague's conclusion that varenicline should be a primary consideration when treating tobacco dependence in people with MDD.

We were surprised by the low abstinence rate achieved by BASC alone. There are several possible explanations. First, BASC asked participants to decrease habitual avoidance to focus on goal-directed behavior. Reducing avoidance increases behavioral sensitivity to punishment, which increases negative affect, thereby potentially making it harder to resist smoking urges. Secondly, many BASC participants struggled to identify and access pleasure in their daily routine. Lack of access was a major issue, with many participants reporting a

limited range of options due to limited resources, disabilities and other structural barriers. Additional intervention to address financial and/or structural barriers might have facilitated pursuit of rewarding activities. Thirdly, reward learning occurs over time, after reward experience. The average of five to six sessions attended may have provided an insufficient dose of one of the more powerful components of BA.

The comparable efficacy of both ST and BASC when added to varenicline suggests that the intensity of behavioral treatment may be as important when treating smokers with MDD as whether the behavioral treatment specifically targets depression. Indeed, findings have been mixed regarding the extent to which integrating CBT for depression with standard behavioral cessation treatment improves outcomes for individuals with MDD. One study showed no effect [79], another study found some support that was limited by greater treatment intensity for the mood management intervention versus standard treatment [80] and a third study showed a positive effect of a multi-component intervention that included mood management training [25].

In conclusion, we found strong evidence that varenicline improved both short- and long-term abstinence rates relative to placebo among racially and socio-economically diverse adults with varied motivation to quit and varied psychiatric presentations. In addition, consistent with the two prior trials focusing upon individuals with stably treated current or past MDD [23, 27], varenicline did not present a safety risk. However, we found no evidence that BASC was more effective than ST in increasing cessation. Indeed, our findings indicate that, at least in the context of intensive treatment delivered primarily by telephone, ST may even be superior to BASC when provided alone, but this potential advantage was not present when added to varenicline. Psychological interventions are a key component of effective treatment for smokers with depressive disorders. Optimizing the effectiveness of these interventions, particularly when combined with pharmacotherapy, should remain an important area of research.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov Identifier: NCT02378714.

AUTHOR CONTRIBUTIONS

Brian Hitsman: Conceptualization (lead); formal analysis (supporting); funding acquisition (lead); investigation (equal); methodology (lead); project administration (equal); resources (equal); supervision (supporting); visualization (lead); writing—original draft (lead); writing—review and editing (equal). **George D. Papandonatos:** Conceptualization (supporting); formal analysis (lead); funding acquisition (supporting); methodology (supporting); software (lead); visualization (supporting); writing—original draft (equal); writing—review and editing (equal). **Jacqueline K. Gollan:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); supervision (lead); validation (supporting); writing—original draft (supporting); writing—review and editing (supporting). **Mark D. Huffman:** Conceptualization (supporting); data curation (supporting); investigation (supporting); methodology (supporting); supervision (supporting); writing—original draft (supporting); writing—review and editing (supporting). **Raymond Niaura:** Conceptualization (supporting); methodology (supporting); writing—review and editing (supporting). **David C. Mohr:** Conceptualization (supporting); methodology (supporting); project administration (supporting); writing—review and editing (supporting). **Anna K. Veluz-Wilkins:** Data curation (supporting); investigation (supporting); project administration (equal); resources (supporting); supervision (supporting); validation (supporting); writing—review and editing (supporting). **Su Fen Lubitz:** Data curation (supporting); investigation (supporting); project administration (supporting); resources (supporting); supervision (supporting); validation (supporting); writing—review and editing (supporting). **Anita Hole:** Data curation (supporting); methodology (supporting); supervision (lead); validation (supporting); writing—review and editing (supporting). **Frank T. Leone:** Data curation (supporting); methodology (supporting); supervision (supporting); writing—review and editing (supporting). **Sadiya S. Khan:** Data curation (supporting); supervision (supporting); writing—review and editing (supporting). **Erica N. Fox:** Data curation (supporting); project administration (equal); resources (supporting); supervision (supporting); validation (supporting); writing—review and editing (supporting). **Anna-Marika Bauer:** Data curation (supporting); investigation (supporting); project administration (supporting); resources (supporting); supervision (supporting); writing—review and editing (supporting). **E. Paul Wileyto:** Formal analysis (supporting); methodology (supporting); resources (supporting); software (supporting); writing—review and editing (supporting). **Joseph Bastian:** Data curation (supporting); investigation (supporting); resources (supporting); writing—review and editing (supporting). **Robert A. Schnoll:** Conceptualization (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (equal); methodology (supporting); project administration (equal); resources (equal); supervision (supporting); writing—original draft (supporting); writing—review and editing (supporting).

ACKNOWLEDGEMENTS

We thank Lawrence H. Price MD for his advice on study design and methodology; Grisel Marie Robles-Schrader MPA and the Northwestern University Center for Community Health's Stakeholder and Community Academic Research Panel for community engagement support; Mita S. Goel MD, MPH for assistance with participant recruitment; and Pfizer for its donation of varenicline and matching placebo. In addition, we thank Amanda R. Mathew PhD and Celine M. Reyes MS for assistance with project coordination; Sarah Boulton MSW, Allison J. Carroll PhD, Charles Culpepper MS, Samantha Giovannetti MA, LSW, Jonnie Handschin BA, Mackenzie Hosie Quinn BA, Nancy A. Jao PhD, Doukessa Lerias MA, Michael Maloney MA, Andrew Miele BA, Matthew Olonoff MS, Sara Price BA, Stephanie Prymas MA, LPC, Emily Turturici BA and Jessica Weisbrot MSW, MPH for their contributions to participant recruitment, assessment, and/or treatment; and Sue Ware BS for database development and management. 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

B.H. has served on scientific advisory boards for Pfizer and received medication and placebo free of charge from Pfizer for the current study. R.A.S. 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. D.C.M. has accepted honoraria and consulting fees from Otsuka Pharmaceuticals, Optum Behavioral Health, Centerstone Research Institute and the One Mind Foundation; royalties from Oxford Press; and has an ownership interest in Adaptive Health, Inc. M.D.H. has patents for combination therapy for the treatment of heart failure. The George Institute for Global Health has a patent, license and has received investment funding with intent to commercialize fixed-dose combination therapy through its social enterprise business, George Medicines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hitsman B, Papandonatos GD, Gollan JK, Huffman MD, Niaura R, Mohr DC, et al. Efficacy and safety of combination behavioral activation for smoking cessation and varenicline for treating tobacco dependence among individuals with current or past major depressive disorder: A 2 × 2 factorial, randomized, placebo-controlled trial. Addiction. 2023;118(9):1710–25. https://doi.org/10.1111/add.16209