Variable Selection and Regression Analysis of Smoking Cessation Outcomes Using Regularization:
A Reanalysis of the BASC-Varenicline Trial Data

Abstract

Background: Individuals with past or present major depressive disorder (MDD) experience unique barriers to smoking cessation. While varenicline has been shown to be more effective than traditional nicotine replacement therapy in achieving abstinence for individuals with and without MDD, its lower effectiveness for those with MDD suggests that MDD-responsive treatment strategies are necessary. A recent determined that varenicline improved abstinence, but BASC did not, either with or without varenicline. In light of this surprising result, we use data from this study to examine baseline variables as potential predictors of end-of-treatment abstinence and moderators of behavioral treatment's effect thereon.

Methods: We examine data from a randomized, placebo-controlled 2x2 factorial design study of 300 smokers with past or present MDD, who received either placebo or varenicline and standard treatment (ST) or behavioral activation for smoking cessation (BASC). Missing data was imputed through multiple imputation. A cross-validated Lasso was applied at the optimally chosen value of lamda for five imputed data sets within n-many bootstrap re-samples.

Results: The participant's Fagerstrom Test for Cigarette Dependence score, complementary reinforcers (i.e., pleasurable events associated with smoking), and the log of the participant's Nicotine Metabolite Ratio were all baseline predictors of abstinence controlling for treatment type. The model demonstrated good discriminative ability (validation AUC=0.78). Our moderator analysis revealed that baseline anhedonia significantly moderated the effect of behavioral activation treatment, with BA showing increased effectiveness for participants with lower anhedonia levels.

Conclusion: Lasso regression identified both meaningful predictors of abstinence and treatment effect moderators with moderately good discrimination power, suggesting potential pathways for treatment personalization in smoking cessation for individuals with MDD. The effectiveness of behavioral activation treatment appears to vary with baseline anhedonia levels, indicating that anhedonia may be an important consideration in treatment selection. However, limitations including the relatively small sample size, which led to convergence issues and challenges handling class imbalance in the outcome, suggest these findings should be validated in larger studies. Future research might benefit from more sophisticated regularization approaches and larger, more diverse samples to better understand treatment effect heterogeneity in this population.

Introduction

More than 30% of individuals with major depressive disorder (MDD) are daily smokers (Han et al. 2022; Smith et al. 2020; Weinberger et al. 2020). These individuals experience certain characteristic barriers to smoking cessation. Compared to smokers without MDD, they tend to be more likely to smoke heavily, to experience greater dependence on smoking, and to consider smoking to be more rewarding than other activities; it may thus be unsurprising that smokers with MDD experience more severe withdrawal symptoms (Breslau, Kilbey, and Andreski 1992; Spring, Pingitore, and McChargue 2003; Weinberger, Desai, and McKee 2010; Lyons et al. 2008). Smoking relapse is also associated with lower experience of reward and cognition, both of which tend to be impaired among those diagnosed with MDD (Leventhal et al. 2009; Cook et al. 2010; Patterson et al. 2009). Even past MDD adversely affects smoking cessation treatment outcomes (Hitsman, Papandonatos, et al. 2013).

Perhaps because of these challenges, individuals with MDD have typically been excluded from smoking treatment clinical trials (Hitsman et al. 2003; Hitsman, Papandonatos, et al. 2013; Talukder et al. 2023). Only six trials have explored smoking cessation in individuals with MDD (Evins et al. 2008; Anthenelli et al. 2013; Thorsteinsson et al. 2001; Hall et al. 2006; Minami et al. 2022; Hitsman et al. 2023), two of which had sample sizes of fewer than 50 participants (Thorsteinsson et al. 2001; Minami et al. 2022).

Additional research evaluating approaches to smoking cessation in this population is necessary. One such approach is treatment with varenicline, a pharmaceutical intervention shown to lessen cravings, withdrawal, withdrawal-related cognitive impairment, and reward from smoking (Patterson et al. 2009; Hitsman, Hogarth, et al. 2013; Perkins et al. 2010; Sofuoglu et al. 2009; West et al. 2008; McClure et al. 2012; Cinciripini et al. 2013). While cessation with varenicline was higher in smokers without any mental health disorders (Anthenelli et al. 2016), one trial of varenicline for individuals with MDD found greater abstinence versus placebo at 52 weeks (28.5% vs. 17.5%) (Anthenelli et al. 2013). However, individuals with mental health disorders, including MDD, are more likely to be prescribed nicotine replacement therapy, a comparatively less effective therapy, than varenicline (Anthenelli et al. 2016; Taylor et al. 2020). This hesitance to prescribing varenicline may stem from a prior boxed warning that, as of 2016, has been removed based on studies evincing the safety of varenicline for individuals with and without mental health disorders (Anthenelli et al. 2016).

The data in our study is derived from a recent randomized, placebo-controlled trial which examined whether the effectiveness of varenicline for smoking cessation in adults with current or past MDD is enhanced by behavioral activation for smoking cessation (BASC) (Hitsman et al. 2023). Behavioral activation (BA) increases reward experience and decreases avoidance-based coping (35-37 Cuijpers, Van Straten, and Warmerdam 2007; Dimidjian et al. 2011; Hopko et al. 2003; MacPherson et al. 2010). A prior pilot study indicated that individuals with elevated depression symptoms, but not MDD, had better cessation results at 26 weeks with BA and nicotine replacement therapy compared to those with standard behavioral treatment (ST) and nicotine replacement therapy (14.3% vs. 0%) (MacPherson et al. 2010).

The Hitsman study from which we draw our data uses a 2x2 factorial design, with 300 participants with past or present MDD treated, over 12 weeks, with BASC or ST alongside placebo or varenciline. Although the Hitsman study found that BASC did not outperform ST with respect to abstinence at 27 weeks, with or without varenicline, it did find that varenicline improved short- and longer-term abstinence compared to placebo (Hitsman et al. 2023). The dual goals of our analysis of the Hitsman et al. (2023) data will be to assess whether and how baseline variables (1) moderate behavioral treatment's effect on end-of-treatment (EOT) abstinence and (2) predict EOT abstinence, controlling for pharmaceutical and behavioral treatments.

In order to accomplish these dual goals, we use regularized linear models. Regularization, also known as shrinkage, reduces variance by fitting a model with all p predictors, with the estimated coefficients shrunken towards zero relative to the least square estimates [Hastie, Tibshirani, and Friedman (2009); pp. 204]. We use this technique here because our goal can be understood as a variable selection problem. The Lasso method of regularization, which comepls some of the coefficients to be exactly equal to zero, can also be used for variable selection [Hastie, Tibshirani, and Friedman (2009); pp. 204, 219]. Best subset regression seeks the optimal subset of predictors by evaluating all possible combinations, thereby ensuring selection of the model with the lowest prediction error, although at a computational cost that increases exponentially with the number of predictors (Hazimeh and Mazumder 2020; Hastie, Tibshirani, and Wainwright 2015). In contrast, L0+L2 regularization combines the sparsity-promoting L0 penalty, which counts the number of non-zero coefficients, with the L2 penalty that shrinks coefficients towards zero without zeroing them, effectively balancing variable selection with the need to manage multicollinearity and enhance model accuracy (Hazimeh and Mazumder 2020; Hastie, Tibshirani, and

Wainwright 2015; Paul 2024). The relaxed lasso, a modification of the Lasso method, initially applies the Lasso to determine a subset of variables by shrinking some coefficients to zero, then refits these selected variables with a reduced or absent Lasso penalty, potentially reducing bias while retaining the variable selection advantage of the original Lasso approach (Meinshausen 2007). L0+L2 and relaxed Lasso are considered the best trade-offs between variable selection and goodness of fit (Paul 2024). Best subset, L0+L2, and relaxed Lasso are more computationally difficult than standard lasso.

Methods

Variables

First, we note that all covariates, other than abstinence (`abst`), are baseline variables. The following variables are binary: pharmacotherapy (`Var`); psychotherapy (`BA`); sex (`sex_ps`); indicators of whether the participant identifies as non-Hispanic white, Black, and/or Hispanic (`NHW`, `Black`, and `Hisp`); whether the individual smokes within five minutes of waking up (`ftcd.5.mins`); other lifetime DSM-5 diagnosis (`otherdiag`); whether the participant takes antidepressant medication (`antidepmed`); current or past MDD (`mde_curr`); and exclusive use of methylated cigarettes (`Only.Menthol`). The numeric variables are age (`age_ps`); cigarettes per day (`cpd_ps`); and Nicotine Metabolism Ratio (`NMR`). All remaining variables are ordinal. However, we treat income (`inc`) and education (`edu`) as ordinal, but (as we discuss below) treat the following variables as numeric: FTCD score (`ftcd_score`); `bdi_score_pq1`; cigarette reward value (`crv_total_pg1`); substitute reinforcer score (`hedonsum_n_pq1`); complementary reinforcer score (`hedonsum_y_pq1`); anhedonia (`shaps_score_pg1`); and readiness to quit smoking (`readiness`).

The `ftcd_score` is the participant's score on the Fagerstrom Test for Cigarette Dependence, a six-item survey intended to evaluate the quantity of cigarette consumption, dependence, and compulsion to smoke; answers are scored and summed to yield a total score of 0-10, with higher scores indicating a greater physical dependence on nicotine (Fagerström 2011).

The `bdi_score_pq1` is the participant's score on the Beck Depression Inventory, or BDI-II, a 21-item survey scored from 0 to 63 measuring the severity of depression, with higher scores indicating greater severity (Beck, Steer, and Brown 1996).

The `crv_total_pq1` score measures the participant's score on a questionnaire measuring preference for smoking over other traditionally rewarding activities, measured on a scale of 0 to 15, where 1 point is added for each time the participant chooses smoking (Spring, Pingitore, and McChargue 2003).

Substitute and complimentary reinforcer scores (`hedonsum_n_pq1` and `hedonsum_y_pg1`) come from a participant's score of the cross-product of frequency (measured from 0 to 2) and level of enjoyableness (0 to 2) for a 45-item version of the Pleasant Events Schedule (MacPhillamy and Lewinsohn 1982); based on the participant's report of whether an event is or is not associated with smoking, it is designated a complementary or substitute reinforcer, the cross products of which are summed.

Anhedonia (`shaps_score_pq1`) is assessed with the 14-item Snaith-Hamilton Pleasure Scale (SHAPS), where 14 statements are ranked on a 4-point Likert scale, with higher scores indicating greater enjoyment of typically rewarding experiences (Snaith et al. 1995).

Nicotine metabolism ratio, otherwise known as nicotine metabolite ratio (`NMR`), is calculated as the ratio of 3'hydroxycotinine [3HC] to cotinine; `NMR` is a biomarker where higher `NMR` is associated with faster metabolism of nicotine (Siegel et al. 2020).

Exploratory Data Analysis

The original paper uses a 2x2 factorial design. However, we choose to keep the treatment variables separate because the sample size is very small and further reducing the sample size to the four groups at issue would significantly limit the Lasso's ability to fit the data. That the 2x2 factorial design is not necessary to answer the research question validates our choice.

In addition to summary statistics available in Table 1 and the correlation matrix, we also inspect univariate histograms (omitted for space) for all variables. Bivariate plots with the outcome are omitted because the outcome is binary. We note that there is still the assumption that there is a linear relationship between the log odds of predictors and the outcome.

Additionally we examine the distribution and association of all variables between levels of `abst`, `BA`, and `Var` (tables omitted for space). When dividing the sample for each variable by `abst` we see that there is a significant difference between those who abstain and those who do no in the `Var`. This is because of the noted effectiveness of the treatment `Var`. We also observe marginal significance in the variable `ftcd_score` with abstainers having lower baseline scores. This could be a confounder, but makes logical sense as higher `ftcd_score` indicates greater dependency which would make it more difficult to abstain. There are no other significant differences in variables between groups of `abst`. Finally, when dividing the sample for each variable by `BA` we see that there are no significant differences in variables between groups of `BA`. Lastly, when dividing the sample for each variable by `Var` we see one significant difference in `abst`, essentially a mirror image of the difference discussed prior.

We note that certain survey variables, specifically `ftcd_score`, `crv_total_pq1`, `readiness`, `shaps_score_pq1`, `hedonsum_y_pq1`, and `hedonsum_n_pq1` are ordinal but will be treated here as either numeric integers or continuous for the purpose of the modeling. This presents a limitation in that we are treating ordinal variables as evenly spaced. Doing so is more or less justifiable for different variables. For example, we are more justified in treating `hedonsum_y_pq1` and `hedonsuum_n_pq1` as continuous, given that each score is made up of the product of two ordinal scales; by using the cross-product, the study authors have made some assumptions about relative scale that obfuscates the ordinal nature of the original.

Nevertheless, treating these variables as ordinal is untenable here, as it would make individual cell sizes incredibly small and lead to parameter proliferation in modeling. Another potential solution would be grouping ordinal variables into discernible levels, as with `inc`, discussed below, but this would take an in-depth understanding of the meaning and spacing for each score that we do not have at present. Said another way, grouping the variables without fully understanding how relative distance between ordinal levels is expressed would lead to our making similar assumptions about the spacing between levels as we make in treating the variables as continuous. We note this is consistent with the handling of survey score variables in Table 1 of the original paper.

To ameliorate the potential loss of accurate fit from treating ordinal variables as numeric, we use polynomial fit for each variable, allowing non-linearities between the log odds ratio for these variables and the outcome. The default contrast handling for ordinal covariates in R is a polynomial contrast. Applying the polynomial score transformation approximates this relationship, without incurring the cost of a parameter for all but one level of the variable.

Table 1: Summary of Variables

Variable	Type	Summary	Normal Distribution	Outlier(s) Present	Skewness	Kurtosis
abst [n (%)]	Categorical	No: 236 (78.67%), Yes: 64 (21.33%)	NA	NA	NA	NA

Variable	Type	Summary	Normal Distribution	Outlier(s) Present	Skewness	Kurtosis
Var [n (%)]	Categorical	Placebo: 136 (45.33%), Varenicline: 164 (54.67%)	NA	NA	NA	NA
BA [n (%)]	Categorical	Standard: 149 (49.67%), BA: 151 (50.33%)	NA	NA	NA	NA
age_ps [Mean (SD) (Quantile)]	Numeric	49.99 (12.6) (41 - 59)	No	No	Left-skewed	Platykurtic
sex_ps [n (%)]	Categorical	Male: 135 (45%), Female: 165 (55%)	NA	NA	NA	NA
NHW [n (%)]	Categorical	No: 195 (65%), Yes: 105 (35%)	NA	NA	NA	NA
Black [n (%)]	Categorical	No: 143 (47.67%), Yes: 157 (52.33%)	NA	NA	NA	NA
Hisp [n (%)]	Categorical	No: 282 (94%), Yes: 18 (6%)	NA	NA	NA	NA
inc [n (%)]	Categorical	Less than $20,000: 110 (37.04%), $20,000–35,000: 68 (22.9%), $35,001–50,000: 46 (15.49%), $50,001–75,000: 38 (12.79%), More than $75,000: 35 (11.78%)	NA	NA	NA	NA
edu [n (%)]	Categorical	Grade School: 1 (0.33%), Some High School: 16 (5.33%), High School Graduate/GED: 76 (25.33%), Some College/Technical School: 116 (38.67%), College Graduate: 91 (30.33%)	NA	NA	NA	NA
ftcd_score [Mean (SD) (Quantile)]	Numeric	5.22 (2.14) (4 - 7)	No	No	Centered	Mesokurtic
ftcd.5.mins [n (%)]	Categorical	No: 162 (54%), Yes: 138 (46%)	NA	NA	NA	NA
bdi_score_w00 [Mean (SD) (Quantile)]	Numeric	18.72 (11.47) (10 - 26)	No	No	Centered	Mesokurtic
cpd_ps [Mean (SD) (Quantile)]	Numeric	15.15 (7.89) (10 - 20)	No	Yes	Right-skewed	Leptokurtic
crv_total_pq1 [Mean (SD) (Quantile)]	Numeric	7.19 (3.7) (5 - 9.75)	No	No	Centered	Platykurtic
hedonsum_n_pq1 [Mean (SD) (Quantile)]	Numeric	22.63 (19.6) (9 - 31)	No	Yes	Right-skewed	Leptokurtic
hedonsum_y_pq1 [Mean (SD) (Quantile)]	Numeric	25.43 (19.42) (12 - 35)	No	Yes	Right-skewed	Leptokurtic
shaps_score_pq1 [Mean (SD) (Quantile)]	Numeric	2.25 (3.16) (0 - 3)	No	Yes	Right-skewed	Leptokurtic
otherdiag [n (%)]	Categorical	No: 167 (55.67%), Yes: 133 (44.33%)	NA	NA	NA	NA
antidepmed [n (%)]	Categorical	No: 218 (72.67%), Yes: 82 (27.33%)	NA	NA	NA	NA
mde_curr [n (%)]	Categorical	Past: 153 (51%), Current: 147 (49%)	NA	NA	NA	NA
NMR [Mean (SD) (Quantile)]	Numeric	0.36 (0.23) (0.21 - 0.47)	No	Yes	Right-skewed	Leptokurtic
Only.Menthol [n (%)]	Categorical	No: 120 (40.27%), Yes: 178 (59.73%)	NA	NA	NA	NA
readiness [Mean (SD) (Quantile)]	Numeric	6.78 (1.24) (6 - 8)	No	No	Centered	Mesokurtic

Note:
Shapiro-Wilk test for normality; Grubb's test for outliers.

Other notable decisions include omission of `Hisp` due to insufficient sample size (18 individuals), which is a limitation of our analysis. We considered taking the three race and ethnicity variables `NHW`, `Black`, and `Hisp` and producing a single race plus ethnicity variable with mutually exclusive groups for non-Hispanic white, non-Hispanic Black, Hispanic, and Other. However because there are only 18 individuals noted

as `Hisp` (and only two of those individuals are `Black`), this hypothetical combined race plus ethnicity variable would've suffered from the same cell size issue as other factors with many levels.

We further note that based on our correlation matrix there is a very high correlation (well over 85%) between `NHW` and `Black`. This issue combined with the issue noted previously lead us to also drop the `NHW` variable. We also note that use of only menthol cigarettes is highly correlated with both `NHW`, `Black`, `inc`, and `edu`. This is a concern, but as menthol cigarette use may be a unique trait and we are conducting regularized regression, we elect to leave this variable in the model and allow the penalty to aid our choice.

We conclude by grouping levels of `edu` and `inc` to limit parameter proliferation and allow for estimation and model convergence, given that Table 1 shows that there is insufficient sample within each level when not grouped. And, to take the log of the one true continuous variable, `NMR`, to encourage normality. Regarding the last decision, we do not assume normality, but note that normalizing transformations can encourage convergence and simplify the loss landscape.

Finally, we note that there is a minor class imbalance issue (~2.1:10). The outcome is somewhat rare, and this could lead to model fitting issues. Correcting for this class imbalance is a potential area for improvement and a limitation.

Figure 1: Correlation Matrix

	abst	Var	BA	age_ps	sex_ps	NHW	Black	Hisp	inc	edu	ftcd_score	ftcd.5.mins	bdi_score_w00	cpd_ps	crv_total_pq1	hedonsum_n_pq1	hedonsum_y_pq1	shaps_score_pq1	otherdiag	antidepmed	mde_curr	NMR	Only.Menthol	readiness
readiness	-0.04	-0.07	-0.04	0.14	0.07	-0.10	0.11	0.02	0.15	0.18	-0.09	-0.00	-0.07	-0.09	-0.18	0.11	0.09	-0.06	-0.05	0.01	-0.05	-0.04	0.03	1.00
Only.Menthol	0.23	0.18	0.15	0.24	0.31	0.66	0.70	0.41	0.59	0.56	0.07	0.30	-0.04	0.03	-0.16	-0.16	0.00	-0.06	0.23	0.15	0.22	-0.09	1.00	0.03
NMR	0.13	0.02	0.00	0.15	0.11	0.24	-0.16	0.03	0.17	0.13	-0.00	-0.07	-0.02	0.00	0.02	-0.01	-0.12	-0.03	-0.04	0.07	-0.05	1.00	-0.09	-0.04
mde_curr	0.32	0.22	0.16	-0.21	0.26	0.08	0.11	0.18	0.48	0.37	0.11	0.09	0.55	-0.02	0.03	-0.26	-0.04	0.19	0.54	0.11	1.00	-0.05	0.22	-0.05
antidepmed	0.09	0.30	0.40	0.08	0.30	0.36	0.30	0.30	0.37	0.35	0.15	0.33	0.06	0.01	0.05	-0.03	0.04	0.01	0.26	1.00	0.11	0.07	0.15	0.01
otherdiag	0.27	0.19	0.16	-0.20	0.20	0.09	0.27	0.17	0.41	0.30	0.04	0.32	0.36	-0.04	0.02	-0.13	0.09	0.13	1.00	0.26	0.54	-0.04	0.23	-0.05
shaps_score_pq1	-0.10	-0.02	-0.01	-0.29	-0.00	0.05	-0.12	0.03	0.07	0.04	0.18	0.10	0.39	0.13	0.28	-0.26	-0.05	1.00	0.13	0.01	0.19	-0.03	-0.06	-0.06
hedonsum_y_pq1	-0.05	-0.10	-0.03	-0.02	0.03	-0.09	0.13	0.01	0.04	0.13	0.11	0.11	-0.08	-0.07	0.05	-0.20	1.00	-0.05	0.09	0.04	-0.04	-0.12	0.00	0.09
hedonsum_n_pq1	0.07	0.03	0.02	0.05	0.00	0.13	-0.17	-0.00	0.24	0.24	-0.28	-0.25	-0.32	-0.08	-0.25	1.00	-0.20	-0.26	-0.13	-0.03	-0.26	-0.01	-0.16	0.11
crv_total_pq1	-0.01	-0.01	0.04	-0.12	0.02	0.21	-0.23	-0.05	0.15	0.19	0.28	0.15	0.15	0.20	1.00	-0.25	0.05	0.28	0.02	0.05	0.03	0.02	-0.16	-0.18
cpd_ps	-0.10	-0.02	0.06	0.13	-0.15	0.14	-0.11	-0.07	0.10	0.10	0.50	0.26	-0.02	1.00	0.20	-0.08	-0.07	0.13	-0.04	0.01	-0.02	0.00	0.03	-0.09
bdi_score_w00	-0.07	0.00	-0.03	-0.29	0.03	-0.00	-0.09	0.07	0.17	0.09	0.11	0.07	1.00	-0.02	0.15	-0.32	-0.08	0.39	0.36	0.06	0.55	-0.02	-0.04	-0.07
ftcd.5.mins	0.27	0.24	0.24	0.07	0.11	0.27	0.34	0.25	0.39	0.43	0.63	1.00	0.07	0.26	0.15	-0.25	0.11	0.10	0.32	0.33	0.09	-0.07	0.30	-0.00
ftcd_score	-0.22	-0.05	-0.02	0.13	-0.01	0.05	-0.00	-0.03	0.09	0.24	1.00	0.63	0.11	0.50	0.28	-0.28	0.11	0.18	0.04	0.15	0.11	-0.00	0.07	-0.09
edu	0.40	0.37	0.31	0.16	0.32	0.52	0.60	0.31	0.53	1.00	0.24	0.43	0.09	0.10	0.19	0.24	0.13	0.04	0.30	0.35	0.37	0.13	0.56	0.18
inc	0.31	0.31	0.32	0.12	0.33	0.54	0.59	0.38	1.00	0.53	0.09	0.39	0.17	0.10	0.15	0.24	0.04	0.07	0.41	0.37	0.48	0.17	0.59	0.15
Hisp	0.17	0.15	0.04	-0.09	0.05	0.43	0.46	1.00	0.38	0.31	-0.03	0.25	0.07	-0.07	-0.05	-0.00	0.01	0.03	0.17	0.30	0.18	0.03	0.41	0.02
Black	0.30	0.28	0.26	0.28	0.36	0.88	1.00	0.46	0.59	0.60	-0.00	0.34	-0.09	-0.11	-0.23	-0.17	0.13	-0.12	0.27	0.30	0.11	-0.16	0.70	0.11
NHW	0.38	0.15	0.27	-0.14	0.39	1.00	0.88	0.43	0.54	0.52	0.05	0.27	-0.00	0.14	0.21	0.13	-0.09	0.05	0.09	0.36	0.08	0.24	0.66	-0.10
sex_ps	0.11	0.17	0.12	0.09	1.00	0.39	0.36	0.05	0.33	0.32	-0.01	0.11	0.03	-0.15	0.02	0.00	0.03	-0.00	0.20	0.30	0.26	0.11	0.31	0.07
age_ps	0.03	-0.04	0.04	1.00	0.09	-0.14	0.28	-0.09	0.12	0.16	0.13	0.07	-0.29	0.13	-0.12	0.05	-0.02	-0.29	-0.20	0.08	-0.21	0.15	0.24	0.14
BA	0.19	0.08	1.00	0.04	0.12	0.27	0.26	0.04	0.32	0.31	-0.02	0.24	-0.03	0.06	0.04	0.02	-0.03	-0.01	0.16	0.40	0.16	0.00	0.15	-0.04
Var	0.53	1.00	0.08	-0.04	0.17	0.15	0.28	0.15	0.31	0.37	-0.05	0.24	0.00	-0.02	-0.01	0.03	-0.10	-0.02	0.19	0.30	0.22	0.02	0.18	-0.07
abst	1.00	0.53	0.19	0.03	0.11	0.38	0.30	0.17	0.31	0.40	-0.22	0.27	-0.07	-0.10	-0.01	0.07	-0.05	-0.10	0.27	0.09	0.32	0.13	0.23	-0.04

Missingness

We examined the amount of missing data by variable and by sample. The most missing data in any singe record is two missing variables. There are seven variables missing data. The most missing data exists in `NMR` with 21 missing values (7%). There are 241 complete cases, which would reduce our sample by 59 records. This strongly suggests the need for imputation. After inspecting the data, we ran Little's

test for MCAR. The null hypothesis for this test is that the data are not MCAR. The p-value was over 0.05, so we cannot reject the null hypothesis. We conclude that there is evidence that these data are missing completely at random. Missing data in covariates will be imputed during the bootstrap process to preserve the already limited sample available.

Modeling

We use a Lasso model to answer both questions at issue. To evaluate baseline variables that predict `abst`, we construct a Lass model that includes all main effects and polynomial terms for score variables. To evaluate baseline moderators of the effect of `BA` on `abst`, we also use a Lasso model, but the model that we use this time includes all main effects and polynomial terms of scores, as well as interactions of those terms with `BA`.

We choose a Lasso model due to its constraints on potential values of the coefficients, introducing desirable bias to the model when performed correctly, which prevent overfitting. We choose not to use L0, L0+L2, or relaxed Lasso: while all three are computationally more difficult and would have more convergence issues than Lasso, the former two also have a harsher penalty (Hazimeh and Mazumder 2020; Hastie, Tibshirani, and Wainwright 2015; Meinshausen 2007).

First, we perform an 80/20 validation training split, where each split has the same proportion of positive outcomes (where `abst`=1). We proceed with the bootstrap of the training data: first, through a bootstrap re-sample of the data, then imputing missing data, and by estimating our Lasso on the imputed bootstrap data as many times as necessary. Coefficients are pooled and confidence intervals are estimated. Bootstrap is used to stabilize estimates due to volatility caused by low sample size and to estimate confidence intervals for coefficients.

After the estimates are derived from the bootstrap procedure, we evaluate the model's performance using the validation data. We tested the model's performance using the pooled estimates on validation data in order to assess calibration and discrimination. For the former, we use calibration plots comparing the model's abstinence predictions to the study's actual results. For the latter, we use AUC and ROC to test whether the model could correctly identify participants who were or were not abstinent.

For the main effects model, enforcement of additional sparsity beyond the Lasso's inherent variable selection was unnecessary, as the number of parameters relative to sample size did not suggest overfitting. However, the moderator model, which included interaction terms with BA treatment, presented a higher risk of overfitting due to the substantially increased number of parameters. Therefore, we implemented additional sparsity criteria for the moderator model: coefficients were retained in the final model only if they were consistently selected (non-zero) across a high proportion of bootstrap iterations (threshold = 0.90). This approach helps prevent overfitting by ensuring that selected moderators demonstrate robust relationships with the outcome across multiple bootstrap samples, rather than capturing spurious associations that might arise from the increased model complexity introduced by interaction terms.

Results

Baseline Variables Predict Abstinence

Results are presented for bootstrapped Lasso regression on outcome abstinence, including main effects of baseline covariates and controlling for other treatments. Only coefficients with confidence intervals not containing zero are presented in the table of results (noted as significant).

There are four significant baseline predictors of abstinence: `ftcd_score`, `Var`, `hedonsum_y_pq1`, and `logNMR`. Varenicline treatment showed a strong positive association with abstinence (OR = 10.84, 95% CI: 1.22-4.11), with participants receiving varenicline having nearly 11 times higher odds of achieving abstinence compared to those receiving placebo, consistent with prior literature on varenicline's efficacy. Additionally, nicotine metabolism rate demonstrated a positive relationship with abstinence outcomes, with each unit increase in log(NMR) associated with 4.28 times higher odds of abstinence (95% CI: 0.63-2.09). That `logNMR` predicts abstinence is also understandable. As noted above, `NMR` indicates faster or slower metabolism of nicotine. Among other potential explanations for this variable's predictive value, individuals with faster nicotine metabolism tend to experience more intense withdrawal symptoms (Liakoni et al. 2019), as well as greater physical dependence and reward (Sofuoglu et al. 2012), presumably making abstinence more difficult. This finding regarding NMR is particularly noteworthy as it appears to diverge from some previous research suggesting faster metabolizers typically experience greater difficulty achieving cessation, though the relationship between metabolism and cessation outcomes is known to be complex and may be treatment-dependent.

Table 2: Lasso Regression Coefficient Estimates

Predictor	Estimate (Median)	Odds Ratio	Lower 2.5%	Upper 97.5%	Proportion Non-Zero	Sig.
VarVarenicline	2.383	10.841	1.223	4.105	1	Yes
poly(ftcd_score, 3, raw = TRUE)1	-3.237	0.039	-6.173	-0.667	1	Yes
poly(ftcd_score, 3, raw = TRUE)2	0.775	2.171	0.134	1.456	1	Yes
poly(ftcd_score, 3, raw = TRUE)3	-0.056	0.946	-0.105	-0.013	1	Yes
poly(hedonsum_y_pq1, 3, raw = TRUE)1	-0.204	0.816	-0.460	-0.021	1	Yes
poly(hedonsum_y_pq1, 3, raw = TRUE)2	0.006	1.006	0.000	0.012	1	Yes
logNMR	1.455	4.284	0.628	2.094	1	Yes

The polynomial variables are difficult to interpret in the same efficient manner as the continuous `logNMR` or binary `Var`, therefore we produce plots to enhance our understanding. The FTCD score (`ftcd_score`) and complementary reinforcer score (`hedonsum_y_pq1`) both demonstrated significant non-linear relationships with abstinence. As visualized in Figure 2, the relationship between FTCD score and abstinence probability follows a complex cubic pattern, with the highest probability of abstinence occurring at low levels of dependence and decreasing non-linearly as the score increases. Similarly, `hedonsum_y_pq1` exhibited a non-linear relationship with abstinence (Figure 3), where the probability of abstinence decreased more steeply at higher levels of complementary reinforcement. As discussed in greater detail above, a higher score for complementary reinforcers denotes greater frequency of and/or more enjoyment of activities associated by the participant with smoking. It makes intuitive sense that, as our results suggest, participants whose more frequent and/or more enjoyable pleasurable events with smoking would have a harder time quitting. For one thing, engaging in those frequent, pleasurable, and smoking-associated activities would likely lead them to wish to smoke. Moreover, they might have fewer opportunities to engage in pleasurable activities not associated with smoking, undermining their ability to find alternative sources of reward. These findings suggest that both nicotine dependence and the degree to which participants associate pleasurable activities with smoking have complex, rather than straightforward linear, relationships with abstention.

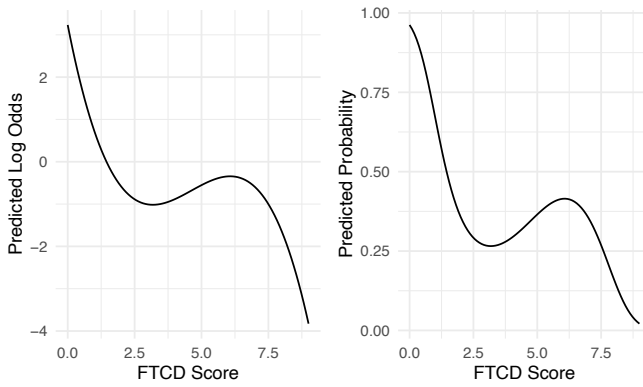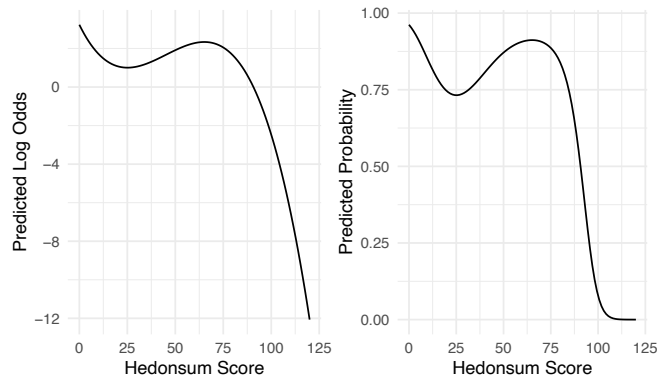Figure 2: Relationship between FTCD Score and Estimates

Figure 3: Relationship between Hedonsum Score and Estimates

Diagnostics

The model's discriminative ability was assessed using ROC curves and calibration plots (Figures 4 and 5). The Lasso model demonstrated good discriminative performance with an AUC of 0.78 on the validation set, though some overfitting is suggested by the higher training AUC of 0.85. The calibration plot reveals generally good agreement between predicted and observed probabilities at lower ranges, but shows increasing uncertainty at higher probability ranges, as evidenced by the widening confidence bands around the Loess curve. This pattern is not unexpected given the class imbalance in our data. The overall calibration suggests the model provides reasonably reliable probability estimates, especially in the more commonly observed lower probability ranges.
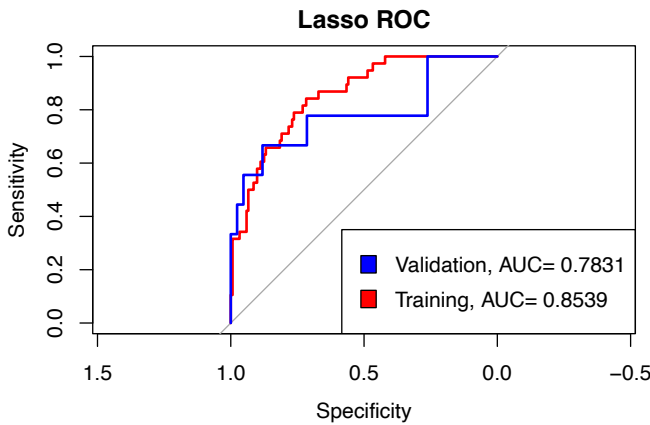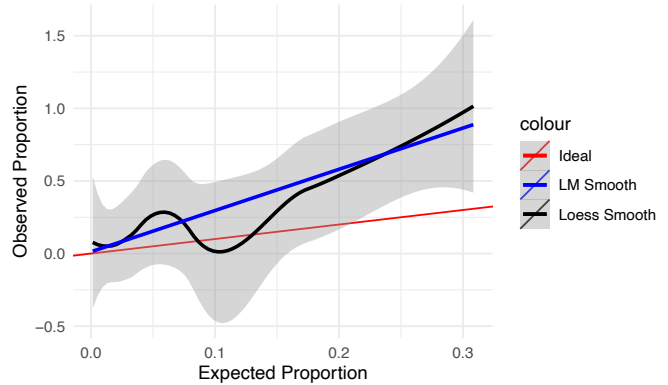
Figure 4: Lasso ROC / AUC Plot

Figure 5: Lasso Calibration Plot on Validation Data

Baseline Variables as Moderators of BA

Results are presented for bootstrapped Lasso regression on the outcome abstinence, with main effects included and unpenalized. Interactions of baseline covariates with BA are included and penalized, allowing the Lasso to select the interaction terms of consequence. Only coefficients with confidence intervals not containing zero are presented in the table of results (noted as significant).

Our moderator analysis revealed that anhedonia `shaps_score_pq1` significantly moderated the effect of BA treatment on abstinence outcomes (Table 3). This relationship was markedly non-linear, as visualized in Figure 6. The diverging curves for standard treatment versus BA demonstrate that the effect of BA

on abstinence varies substantially based on baseline anhedonia levels. For participants with higher SHAPS scores (indicating higher anhedonia), BA and standard treatment showed similar effectiveness. However, as baseline anhedonia decreased, BA demonstrated increasingly superior outcomes compared to standard treatment, suggesting that BA may be particularly beneficial for individuals experiencing lower levels of anhedonia. This finding is somewhat paradoxical given BA's proposed mechanism of action in increasing reward experience and decreasing avoidance-based coping. We might expect those with higher anhedonia to do better with BA, but we observe the opposite. The model also confirmed the robust effect of varenicline (OR = 816.00, 95% CI: 3.22-15.39), though the wide confidence interval suggests considerable uncertainty in the effect size estimate.

Table 3: Lasso Regression Coefficient Estimates

Predictor	Estimate (Median)	Odds Ratio	Lower 2.5%	Upper 97.5%	Proportion Non-Zero	Sig.
VarVarenicline	6.704	816.001	3.219	15.392	1	Yes
BABA:poly(shaps_score_pq1, 3, raw = TRUE)1	4.121	61.627	0.370	19.145	1	Yes

Figure 6: Relationship between SHAPS Score and Estimates
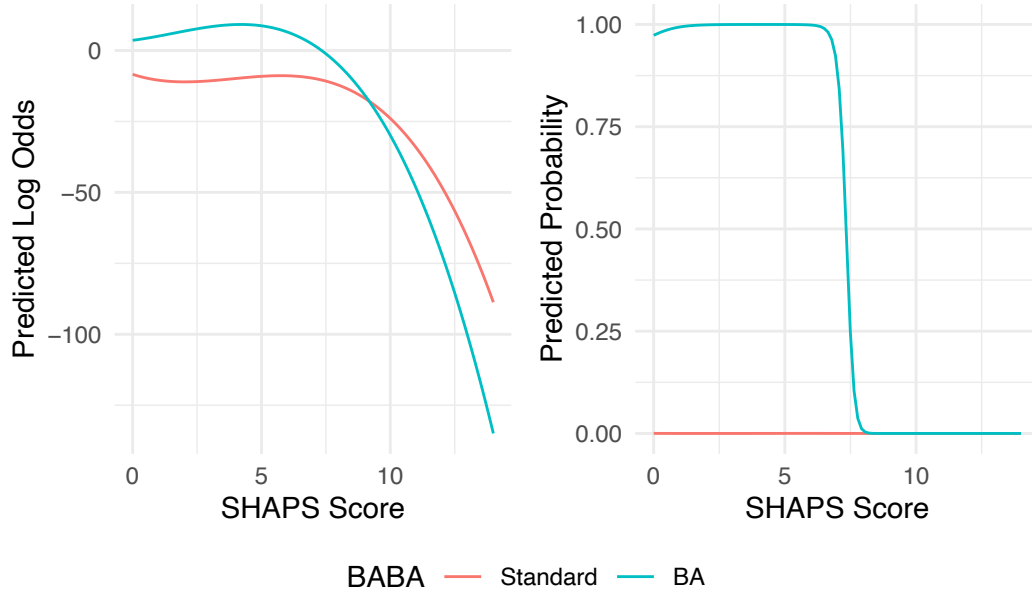
Diagnostics

The diagnostic plots for the moderator analysis (Figures 7 and 8) suggest more modest model performance compared to our main effects model. The ROC curves show fair discriminative ability with an AUC of 0.59 on the validation set and 0.67 on the training set. This decreased performance relative to our previous model likely reflects the increased complexity introduced by interaction terms and the inherent difficulty in predicting treatment effect heterogeneity especially in small samples. The calibration plot reveals substantial deviation from the ideal diagonal, with the model showing a tendency toward over-optimistic predictions in the mid-range probabilities and under-prediction at higher probabilities. The wide confidence bands around the Loess curve indicate considerable uncertainty in these predictions. These diagnostics suggest that while the model successfully identified a meaningful treatment-moderator interaction with anhedonia, its overall predictive accuracy is limited and its probability estimates should be interpreted with caution.
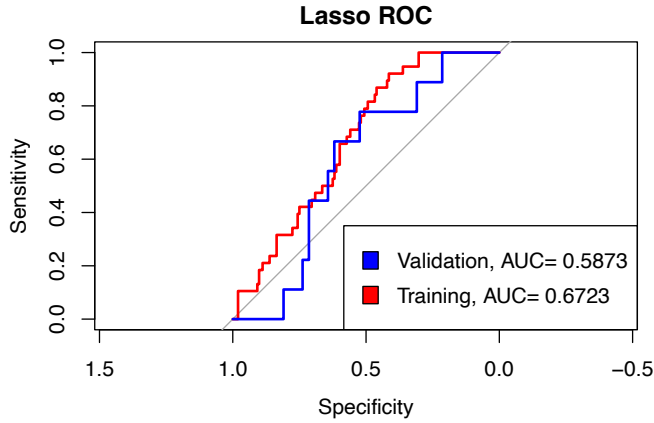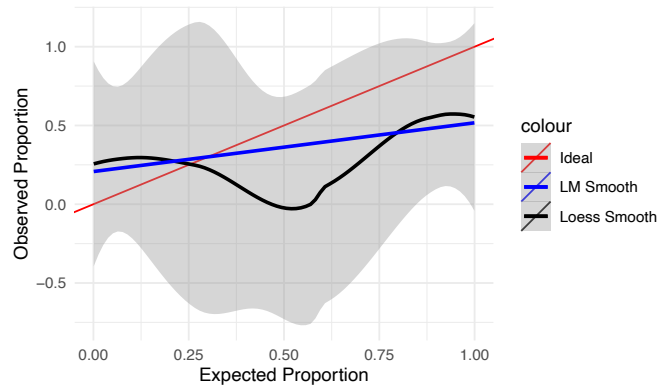
Figure 7: Lasso ROC / AUC Plot

Figure 8: Lasso Calibration Plot on Validation Data

Conclusion

In this reanalysis of the BASC-Varenicline trial data, we identified several important predictors of smoking cessation success among individuals with current or past MDD. Our primary analysis confirmed varenicline's strong positive effect on abstinence and revealed complex non-linear relationships between cessation success and baseline characteristics including nicotine dependence (FTCD score) and complementary reinforcement. Notably, higher nicotine metabolism rates were associated with improved cessation outcomes, a finding that warrants further investigation given its divergence from some previous research. Our moderator analysis yielded a particularly valuable clinical insight: the effectiveness of Behavioral Activation treatment varied significantly with baseline anhedonia levels, with BA showing superior outcomes for participants experiencing lower levels of anhedonia.

Several limitations of our analysis warrant discussion. First, our analytical approach was constrained by sample size limitations, which led to the exclusion of Hispanic ethnicity data due to insufficient representation (n=18) and necessitated the grouping of educational and income categories to ensure model convergence. Second, the class imbalance in our outcome (21.33% abstinent) posed challenges for model fitting and likely contributed to the decreased accuracy of predictions at higher probability ranges, particularly in our moderator analysis. Third, convergence issues stemming from our relatively small sample size and numerous dichotomous variables limited our ability to employ more sophisticated regularization approaches. Finally, given more time larger bootstrap runs would be welcome. Future analyses with larger samples might benefit from exploring alternative methods such as L0 best subset selection, L0+L2 regularization, relaxed Lasso, or group Lasso, which could potentially offer improved variable selection and prediction accuracy.

Despite these limitations, our findings suggest that baseline characteristics, particularly anhedonia levels, could inform the personalization of smoking cessation treatments for individuals with current or past MDD. The identified moderating effect of anhedonia on BA treatment efficacy may be valuable for clinical decision-making, though the modest predictive performance of our moderator model suggests that additional research is needed to validate and refine these findings.

References

Anthenelli, Robert M, Neal L Benowitz, Robert West, Lisa St Aubin, Thomas McRae, David Lawrence, John Ascher, Cristina Russ, Alok Krishen, and A Eden Evins. 2016. "Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers with and Without Psychiatric Disorders (EAGLES): A Double-Blind, Randomised, Placebo-Controlled Clinical Trial." *The Lancet* 387 (10037): 2507–20.

Anthenelli, Robert M, Chad Morris, Tanya S Ramey, Sarah J Dubrava, Kostas Tsilkos, Cristina Russ, and Carla Yunis. 2013. "Effects of Varenicline on Smoking Cessation in Adults with Stably Treated Current or Past Major Depression: A Randomized Trial." *Annals of Internal Medicine* 159 (6): 390–400.

Beck, Aaron T, Robert A Steer, and Gregory Brown. 1996. "Beck Depression Inventory–II." *Psychological Assessment.*

Breslau, Naomi, M Marlyne Kilbey, and Patricia Andreski. 1992. "Nicotine Withdrawal Symptoms and Psychiatric Disorders: Findings from an Epidemiologic Study of Young Adults." *The American Journal of Psychiatry* 149 (4): 464–69.

Cinciripini, Paul M, Jason D Robinson, Maher Karam-Hage, Jennifer A Minnix, Cho Lam, Francesco Versace, Victoria L Brown, Jeffrey M Engelmann, and David W Wetter. 2013. "Effects of Varenicline and Bupropion Sustained-Release Use Plus Intensive Smoking Cessation Counseling on Prolonged Abstinence from Smoking and on Depression, Negative Affect, and Other Symptoms of Nicotine Withdrawal." *JAMA Psychiatry* 70 (5): 522–33.

Cook, Jessica, Bonnie Spring, Dennis McChargue, and Neal Doran. 2010. "Effects of Anhedonia on Days to Relapse Among Smokers with a History of Depression: A Brief Report." *Nicotine & Tobacco Research* 12 (9): 978–82.

Cuijpers, Pim, Annemieke Van Straten, and Lisanne Warmerdam. 2007. "Behavioral Activation Treatments of Depression: A Meta-Analysis." *Clinical Psychology Review* 27 (3): 318–26.

Dimidjian, Sona, Manuel Barrera Jr, Christopher Martell, Ricardo F Muñoz, and Peter M Lewinsohn. 2011. "The Origins and Current Status of Behavioral Activation Treatments for Depression." *Annual Review of Clinical Psychology* 7 (1): 1–38.

Evins, A Eden, Melissa A Culhane, Jonathan E Alpert, Joel Pava, Bruce S Liese, Amy Farabaugh, and Maurizio Fava. 2008. "A Controlled Trial of Bupropion Added to Nicotine Patch and Behavioral Therapy for Smoking Cessation in Adults with Unipolar Depressive Disorders." *Journal of Clinical Psychopharmacology* 28 (6): 660–66.

Fagerström, Karl. 2011. "Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence." *Nicotine & Tobacco Research* 14 (1): 75–78.

Hall, Sharon M, Janice Y Tsoh, Judith J Prochaska, Stuart Eisendrath, Joseph S Rossi, Colleen A Redding, Amy B Rosen, Marc Meisner, Gary L Humfleet, and Julie A Gorecki. 2006. "Treatment for Cigarette Smoking Among Depressed Mental Health Outpatients: A Randomized Clinical Trial." *American Journal of Public Health* 96 (10): 1808–14.

Han, Beth, Nora D Volkow, Carlos Blanco, Douglas Tipperman, Emily B Einstein, and Wilson M Compton. 2022. "Trends in Prevalence of Cigarette Smoking Among US Adults with Major Depression or Substance Use Disorders, 2006-2019." *Jama* 327 (16): 1566–76.

Hastie, Trevor, Robert Tibshirani, and Jerome Friedman. 2009. "An Introduction to Statistical Learning."

Hastie, Trevor, Robert Tibshirani, and Martin Wainwright. 2015. "Statistical Learning with Sparsity." *Monographs on Statistics and Applied Probability* 143 (143): 8.

Hazimeh, Hussein, and Rahul Mazumder. 2020. "Fast Best Subset Selection: Coordinate Descent and Local Combinatorial Optimization Algorithms." *Operations Research* 68 (5): 1517–37.

Hitsman, Brian, Belinda Borrelli, Dennis E McChargue, Bonnie Spring, and Raymond Niaura. 2003. "History of Depression and Smoking Cessation Outcome: A Meta-Analysis." *Journal of Consulting*

and Clinical Psychology 71 (4): 657.

Hitsman, Brian, Lee Hogarth, Li-Jung Tseng, Jordan C Teige, William G Shadel, Dana Britt DiBenedetti, Spencer Danto, Theodore C Lee, Lawrence H Price, and Raymond Niaura. 2013. "Dissociable Effect of Acute Varenicline on Tonic Versus Cue-Provoked Craving in Non-Treatment-Motivated Heavy Smokers." *Drug and Alcohol Dependence* 130 (1-3): 135–41.

Hitsman, Brian, George D Papandonatos, Jacqueline K Gollan, Mark D Huffman, Raymond Niaura, David C Mohr, Anna K Veluz-Wilkins, et al. 2023. "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* 118 (9): 1710–25.

Hitsman, Brian, George D Papandonatos, Dennis E McChargue, Andrew DeMott, María José Herrera, Bonnie Spring, Belinda Borrelli, and Raymond Niaura. 2013. "Past Major Depression and Smoking Cessation Outcome: A Systematic Review and Meta-Analysis Update." *Addiction* 108 (2): 294–306.

Hopko, Derek R, CW Lejuez, Kenneth J Ruggiero, and Georg H Eifert. 2003. "Contemporary Behavioral Activation Treatments for Depression: Procedures, Principles, and Progress." *Clinical Psychology Review* 23 (5): 699–717.

Leventhal, Adam M, Andrew J Waters, Christopher W Kahler, Lara A Ray, and Steve Sussman. 2009. "Relations Between Anhedonia and Smoking Motivation." *Nicotine & Tobacco Research* 11 (9): 1047–54.

Liakoni, Evangelia, Kathryn C Edwards, Gideon St. Helen, Natalie Nardone, Delia A Dempsey, Rachel F Tyndale, and Neal L Benowitz. 2019. "Effects of Nicotine Metabolic Rate on Withdrawal Symptoms and Response to Cigarette Smoking After Abstinence." *Clinical Pharmacology & Therapeutics* 105 (3): 641–51.

Lyons, Michael, Brian Hitsman, Hong Xian, Matthew S Panizzon, Beth A Jerskey, Susan Santangelo, Michael D Grant, et al. 2008. "A Twin Study of Smoking, Nicotine Dependence, and Major Depression in Men." *Nicotine & Tobacco Research* 10 (1): 97–108.

MacPherson, Laura, Matthew T Tull, Alexis K Matusiewicz, Samantha Rodman, David R Strong, Christopher W Kahler, Derek R Hopko, Michael J Zvolensky, Richard A Brown, and CW3108050 Lejuez. 2010. "Randomized Controlled Trial of Behavioral Activation Smoking Cessation Treatment for Smokers with Elevated Depressive Symptoms." *Journal of Consulting and Clinical Psychology* 78 (1): 55.

MacPhillamy, Douglas J, and Peter M Lewinsohn. 1982. "The Pleasant Events Schedule: Studies on Reliability, Validity, and Scale Intercorrelation." *Journal of Consulting and Clinical Psychology* 50 (3): 363.

McClure, Erin A, Ryan G Vandrey, Matthew W Johnson, and Maxine L Stitzer. 2012. "Effects of Varenicline on Abstinence and Smoking Reward Following a Programmed Lapse." *Nicotine & Tobacco Research* 15 (1): 139–48.

Meinshausen, Nicolai. 2007. "Relaxed Lasso." *Computational Statistics & Data Analysis* 52 (1): 374–93.

Minami, Haruka, Shadi Nahvi, Julia H Arnsten, Hannah R Brinkman, Monica Rivera-Mindt, David W Wetter, Erika Litvin Bloom, et al. 2022. "A Pilot Randomized Controlled Trial of Smartphone-Assisted Mindfulness-Based Intervention with Contingency Management for Smokers with Mood Disorders." *Experimental and Clinical Psychopharmacology* 30 (5): 653.

Patterson, Freda, Christopher Jepson, Andrew A Strasser, James Loughead, Kenneth A Perkins, Ruben C Gur, Joseph M Frey, Steven Siegel, and Caryn Lerman. 2009. "Varenicline Improves Mood and Cognition During Smoking Abstinence." *Biological Psychiatry* 65 (2): 144–49.

Paul, Alice. 2024. "PHP 2550 - Variable Selection."

Perkins, Kenneth A, Melissa Mercincavage, Carolyn A Fonte, and Caryn Lerman. 2010. "Varenicline's

Effects on Acute Smoking Behavior and Reward and Their Association with Subsequent Abstinence." *Psychopharmacology* 210: 45–51.

Siegel, Scott D, Caryn Lerman, Alex Flitter, and Robert A Schnoll. 2020. "The Use of the Nicotine Metabolite Ratio as a Biomarker to Personalize Smoking Cessation Treatment: Current Evidence and Future Directions." *Cancer Prevention Research* 13 (3): 261–72.

Smith, Philip H, Mohammad Chhipa, Josef Bystrik, Jordan Roy, Renee D Goodwin, and Sherry A McKee. 2020. "Cigarette Smoking Among Those with Mental Disorders in the US Population: 2012–2013 Update." *Tobacco Control* 29 (1): 29–35.

Snaith, R Philip, Max Hamilton, S Morley, A Humayan, D Hargreaves, and P Trigwell. 1995. "A Scale for the Assessment of Hedonic Tone the Snaith–Hamilton Pleasure Scale." *The British Journal of Psychiatry* 167 (1): 99–103.

Sofuoglu, Mehmet, Aryeh I Herman, Marc Mooney, and Andrew J Waters. 2009. "Varenicline Attenuates Some of the Subjective and Physiological Effects of Intravenous Nicotine in Humans." *Psychopharmacology* 207: 153–62.

Sofuoglu, Mehmet, Aryeh I Herman, Haleh Nadim, and Peter Jatlow. 2012. "Rapid Nicotine Clearance Is Associated with Greater Reward and Heart Rate Increases from Intravenous Nicotine." *Neuropsychopharmacology* 37 (6): 1509–16.

Spring, Bonnie, Regina Pingitore, and Dennis E McChargue. 2003. "Reward Value of Cigarette Smoking for Comparably Heavy Smoking Schizophrenic, Depressed, and Nonpatient Smokers." *American Journal of Psychiatry* 160 (2): 316–22.

Talukder, Saki Rubaiya, Julia M Lappin, Veronica Boland, Hayden McRobbie, and Ryan James Courtney. 2023. "Inequity in Smoking Cessation Clinical Trials Testing Pharmacotherapies: Exclusion of Smokers with Mental Health Disorders." *Tobacco Control* 32 (4): 489–96.

Taylor, Gemma MJ, Taha Itani, Kyla H Thomas, Dheeraj Rai, Tim Jones, Frank Windmeijer, Richard M Martin, Marcus R Munafò, Neil M Davies, and Amy E Taylor. 2020. "Prescribing Prevalence, Effectiveness, and Mental Health Safety of Smoking Cessation Medicines in Patients with Mental Disorders." *Nicotine and Tobacco Research* 22 (1): 48–57.

Thorsteinsson, Haraldur S, J Christian Gillin, Christi A Patten, Shahrokh Golshan, Laura D Sutton, Sean Drummond, Camellia P Clark, John Kelsoe, and Mark Rapaport. 2001. "The Effects of Transdermal Nicotine Therapy for Smoking Cessation on Depressive Symptoms in Patients with Major Depression." *Neuropsychopharmacology* 24 (4): 350–58.

Weinberger, Andrea H, Michael O Chaiton, Jiaqi Zhu, Melanie M Wall, Deborah S Hasin, and Renee D Goodwin. 2020. "Trends in the Prevalence of Current, Daily, and Nondaily Cigarette Smoking and Quit Ratios by Depression Status in the US: 2005–2017." *American Journal of Preventive Medicine* 58 (5): 691–98.

Weinberger, Andrea H, Rani A Desai, and Sherry A McKee. 2010. "Nicotine Withdrawal in US Smokers with Current Mood, Anxiety, Alcohol Use, and Substance Use Disorders." *Drug and Alcohol Dependence* 108 (1-2): 7–12.

West, Robert, Christine L Baker, Joseph C Cappelleri, and Andrew G Bushmakin. 2008. "Effect of Varenicline and Bupropion SR on Craving, Nicotine Withdrawal Symptoms, and Rewarding Effects of Smoking During a Quit Attempt." *Psychopharmacology* 197: 371–77.