

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work

### **eMethod 1. Stratification**

Participants were stratified by a single categorical predictor that was a combination of psychiatric disorder and type of psychiatric medication in all abstinence and symptom models. Thus, the 87 randomized participants were characterized as either having a diagnosis of bipolar disorder (n=10), or having a diagnosis of schizophrenia spectrum disorder and taking conventional antipsychotics for Sz (n=8), atypical antipsychotics for Sz (n=52), or clozapine for Sz (n=17).

Participants with bipolar disorder did not differ in either point prevalence or continuous abstinence or psychiatric symptoms (SANS, BPRS) or BMI or health related quality of life (SF-12) from any of the schizophrenia treatment groups.

### **eMethod 2. Rater training and inter-rater reliability**

Assessors were trained for administration and scoring of clinical rating scales. For Brief Psychiatric Rating Scale and Schedule for Assessment of Negative Symptoms, assessors attained agreement with gold standard ratings (ICC2= 0.85 ±1 point) on ten videotaped interviews prior to assessing study participants. For Calgary Depression Scale for Schizophrenia and Young Mania Rating Scale, assessors submitted audiotaped recordings of ≥2 interviews and received feedback on their administration and scoring by experienced raters. To prevent rater drift and assess ongoing inter-rater reliability, assessors submitted monthly ratings of audio/videotaped interviews and received feedback on administration and scoring on monthly conference calls.

### **eResults 1. Prevalence ratios for primary abstinence outcomes**

The 7-day, point-prevalence abstinence rate at week-52, the primary outcome measure, was 60%(24/40) in the extended-duration varenicline+CBT group as compared with 19%(9/47) in the placebo+CBT group,  $p=0.0007$ ; (prevalence ratio (PR): 2.8; 95% CI: 1.5-4.9) and at week-64 (45%(18/40) vs. 13%(6/47);  $p=0.0022$ ; PR: 3.8, 95%CI: 1.6-8.9). The continuous abstinence rate was also higher among those taking varenicline than among those assigned to placebo during relapse-prevention treatment, weeks 12-52, (45%(18/40) vs. 15%(7/47);  $p=0.0040$ ; PR: 3.0; 95%CI: 1.4–6.3)

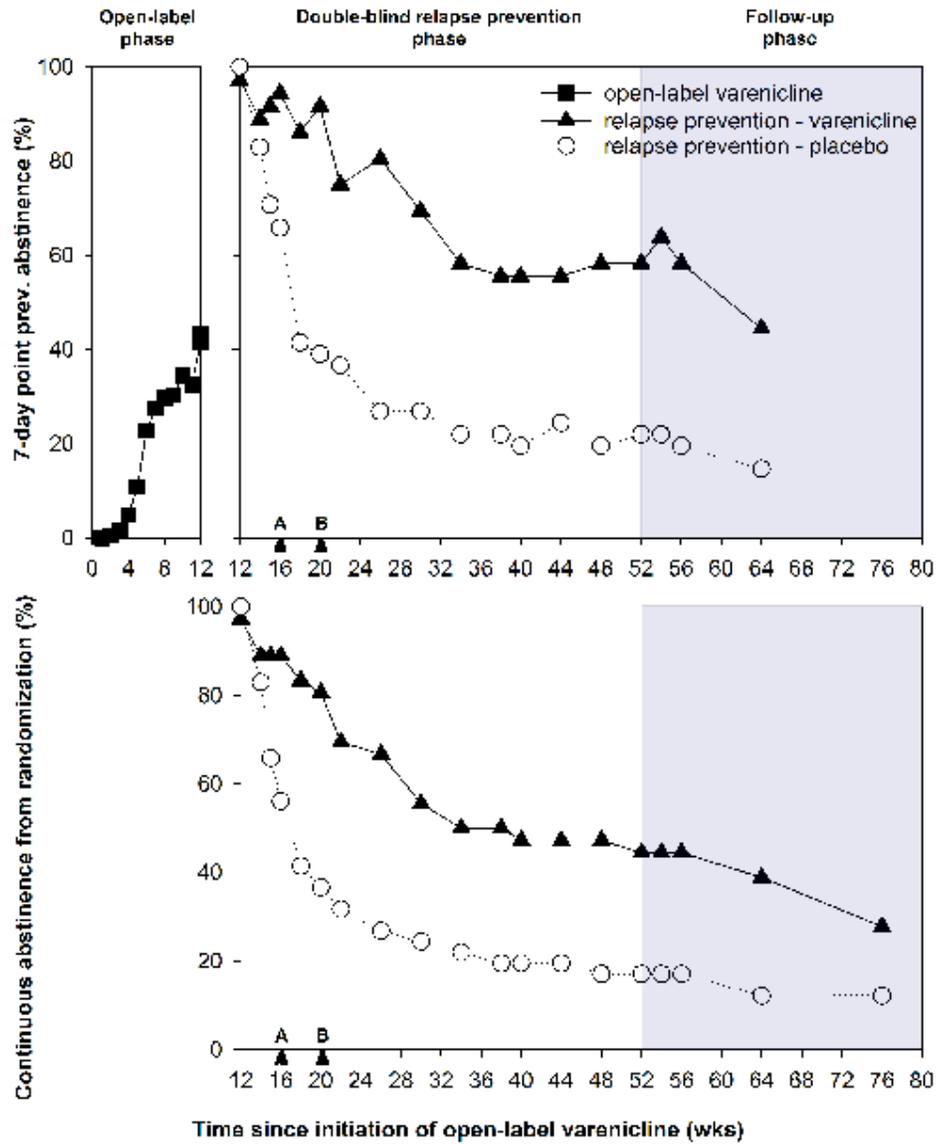
### **eResults 2. Smoking Outcomes in Schizophrenia Participants**

Analyzing the abstinence data for participants diagnosed with schizophrenia spectrum disorder only (i.e., excluding those with bipolar disorder), the 7-day, point-prevalence abstinence rate at week-52, a priori primary outcome measure, was 58%(21/36) in the extended-duration varenicline+CBT group as compared with 22%(9/41) in the placebo+CBT group, exact  $p=0.0012$ , (OR: 3.3; 95%CI: 1.2–10.0).

Expressed as a prevalence ratio, the 7-day, point-prevalence abstinence rate at week-52 for participants diagnosed with schizophrenia spectrum disorder only was higher in those treated with varenicline+CBT than those assigned to placebo+CBT (PR: 2.5; 95% CI: 1.4-4.5;  $p=0.0019$ ).

Similarly, in the primary analysis of continuous abstinence excluding participants with bipolar disorder, the continuous abstinence rate was higher in the varenicline group than the placebo group during relapse-prevention treatment, weeks 12-52, (44%(16/36) vs. 17%(7/41); exact  $p=0.0122$ ; OR: 3.9; 95%CI: 1.2–13.8) Expressed as a prevalence ratio, the continuous abstinence rate was higher in the varenicline group than the placebo group during relapse-prevention treatment, weeks 12-52; (PR: 2.6; 95%CI: 1.3–5.5;  $p=0.0099$ ) (eFigure 1).

**eFigure 1. Point prevalence and continuous abstinence rates during open, randomized and follow-up phases in participants with schizophrenia only.**

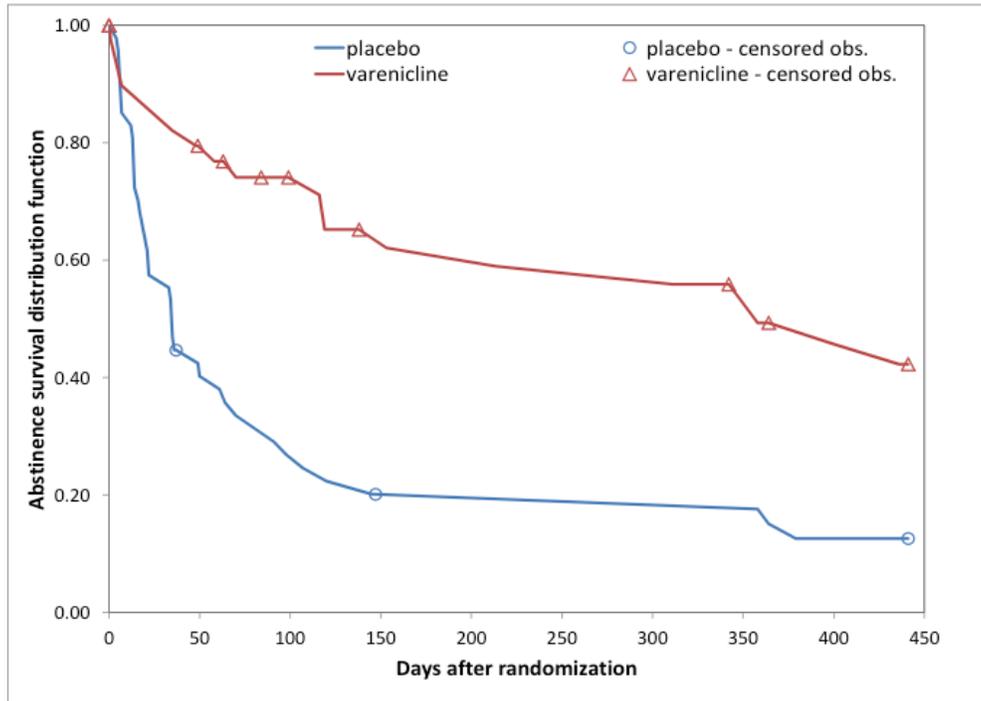


#### **eResults 4. Time to relapse**

The time to first smoking relapse was assessed with the Kaplan-Meier product-limit estimator, and the hazard ratio of relapse was estimated via a Cox proportional hazards regression model. For these analyses, time to first relapse was defined as the date of the study visit at which a participant self-reported his/her first relapse or when their expired CO exceeded 9ppm, whichever came sooner, minus the date of randomization. For participants who did not relapse, time to relapse was censored on the date of the follow-up phone call at week 76 or the date of their last study visit (if early termination). In the proportional hazards regression model, the time to first relapse was modeled with treatment, study site, and diagnosis / antipsychotic medication treatment as independent predictors. We also tested baseline scores of negative symptoms (SANS composite) and psychiatric symptoms (BPRS total) as covariates in each model, but because neither variable was significant in either model ( $p>0.2$ ), we dropped them from the final model.

Participants treated with varenicline in the relapse prevention phase had a significantly longer time to first relapse than participants treated with placebo (Log-rank  $\chi^2=16.0$ ,  $p<0.0001$ ), and neither site nor diagnosis / type of antipsychotic medication significantly predicted time to first relapse. The median time to first relapse was 35 days in the placebo group (95% CI: 21-64; Q1=14, Q3=107, range: 4-441), and 358 days in the varenicline group (95% CI: 119-N/A; Q1=70, Q3=N/A, range: 1-441). Relapse was three times more likely in the placebo group than in the varenicline group ( $\chi^2=15.5$ ,  $p=0.0002$ ; hazard ratio (HR): 0.33; 95% CI: 0.19-0.57), and neither site (Wald  $\chi^2=0.3$ ,  $df=2$ ,  $p=0.86$ ), nor diagnosis / type of antipsychotic medication (Wald  $\chi^2=4.2$ ,  $df=3$ ,  $p=0.24$ ) significantly affected relapse (eFigure 2)

**eFigure 2.** Survival After Abstinence



Legend: SANS = Schedule for Assessment of Negative Symptoms, WSWS = Wisconsin Smoking Withdrawal Scale, YMRS = Young Mania Rating Scale and was completed only in participants with bipolar disorder, MADRS = Montgomery-Asberg Depression Rating Scale and was also completed only in participants with bipolar disorder

### **eResults 5. Sensitivity analyses**

While 26 of 87 participants dropped out of the study during the relapse prevention phase, and drop out was uneven (7 on varenicline and 19 on placebo), all but 8 who dropped out had relapsed prior to drop out (6 had been assigned to varenicline and 2 to placebo). Thus for the continuous abstinence outcome, we imputed missing abstinence data for 26 participants as relapsed, and 8 of these had not relapsed prior to drop out. We conducted a sensitivity analysis for the assumption of relapsed status for participants who dropped out who had been continuously abstinent prior to dropout. In this analysis, the 6 who had been assigned to varenicline were considered relapsed at the time of drop out and the two who had been assigned to placebo were considered continuously abstinent through week 52. Treatment effects on continuous abstinence rates remained significant but with smaller odds ratios. In the sensitivity analyses of continuous abstinence, in which abstinent drop-outs were considered abstinent in the placebo group but relapsed in the varenicline group, the continuous abstinence rate was higher in the varenicline group than the placebo group during relapse-prevention treatment, weeks 12-52, (45% (18/40) vs. 19% (9/47); exact  $p=0.0122$ ; OR: 3.3; 95% CI: 1.2–10.0).

The pre-specified primary analysis considered dropouts as smokers because this was considered the most likely scenario. However, we performed multiple imputation as a sensitivity analysis the primary outcome, 7-day point prevalence abstinence. Multiple imputation assumes that someone who drops out at a visit has the same chance of smoking as a person who doesn't drop out at that visit if they have the same

smoking history at previous visits. We used the R package “mice” to multiply impute patients smoking status at week 52.<sup>1</sup> We multiply imputed the missing data separately for each treatment group. The imputations did not account for the stratification. The results were as follows: For the placebo group, the five imputations for the abstinence rate were 35%, 32%, 30%, 31% and 30%. Using the formula for estimation using multiple imputation, the estimated 7-day point prevalence abstinence rate at week 52 was 31.5% with a standard error of 7.0% in the placebo group. For the treatment group, the five imputations for the abstinence rate were 78%, 75%, 78%, 78% and 73%, with a mean abstinence rate of 76% and a standard error of 7.1%. The p-value for the treatment effect would be <0.0001, indicating a significantly higher 7-day point-prevalence abstinence in the varenicline group than the placebo group at week 52 with multiple imputation of missing data from participants who dropped out prior to week 52.

Confidence intervals on the risk ratio.

The primary analysis was to give confidence intervals on the odds ratio because exact small sample confidence intervals can be computed. Since odds ratios are not easy to interpret, we calculated the confidence intervals on the risk ratio using a log-linear model. The estimated risk-ratio is 3.13 with a 95% confidence interval of from 1.65 to 5.94. This isn't corrected for stratification.<sup>2</sup>

#### **eResults 6. Reasons for Psychiatric Hospitalizations**

The five psychiatric hospitalizations for participants on placebo were for depressed mood and discontinuation of antipsychotic medications, for suicidal ideation, for worsened psychosis and for worsened psychosis and marijuana MJ intoxication, and for manic symptoms. The two psychiatric hospitalizations in those on varenicline were for depressed mood, and for worsened psychotic symptoms. Both participants stayed on study medications and remained in the study.

**Figure 3. Negative, Nicotine Withdrawal, Manic, and Depressive Symptoms by Time and Treatment**

