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Maintenance pharmacotherapy normalizes the relapse curve in recently abstinent tobacco smokers with schizophrenia and bipolar disorder

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ABSTRACT

Objective: To compare the effect of maintenance pharmacotherapy on sustained abstinence rates between recently abstinent smokers with schizophrenia and bipolar disorder (SBD) and general population smokers without psychiatric illness.

Method: We performed a person-level, pooled analysis of two randomized controlled trials of maintenance varenicline, conducted in adult smokers with SBD and general population smokers, controlling for severity of dependence. Smokers abstinent after 12-weeks of open varenicline treatment were randomly assigned to ≥12-weeks maintenance varenicline or identical placebo.

Results: In those assigned to maintenance placebo, the abstinence rate at week-24 was lower in those with SBD than for those without psychiatric illness (29.4 ± 1.1% vs. 61.8 ± 0.4%, OR:0.26, 95% CI: 0.13, 0.52, $p < 0.001$). In smokers assigned to maintenance pharmacotherapy, however, there was no effect of diagnosis on abstinence rates at week-24 (87.2 ± 0.8% vs. 81.9 ± 0.2%, OR: 1.68, 95% CI: 0.53, 5.32, $p = 0.38$). Time to first lapse was shortest in those with SBD assigned to maintenance placebo (Q1 = 12 days, 95%CI: 4, 16), longer in those without psychiatric illness assigned to maintenance placebo (Q1 = 17 days, 95%CI: 17, 29), still longer in general-population smokers assigned to maintenance varenicline (Q1 = 88, 95% CI:58,91, and longest in those with SBD who received maintenance varenicline (Q1 > 95 days, 95%CI:non-est), ($X^2_{3df} = 96.99$, $p < 0.0001$; all pairwise comparisons $p < 0.001$).

Conclusions: Following a standard 12-week course of pharmacotherapy, people with schizophrenia and bipolar disorder were more likely to relapse to smoking without maintenance varenicline treatment. Maintenance pharmacotherapy could improve longer-term tobacco abstinence rates and reduce known smoking-related health disparities in those with SMI.

1. Introduction

Relapse to tobacco smoking following initial abstinence is a significant problem with no accepted treatment (Hajek et al. 2013). Relapse rates at one-year are 31–59% among recently abstinent smokers in the general population (Gonzales et al. 2006; Jorenby et al. 2006; Jorenby et al. 1999; Oncken et al. 2006; Rigotti et al. 2010; Tashkin et al. 2011) and 60–100% among recently abstinent smokers with schizophrenia spectrum disorders (Dale Horst et al. 2005; Evins et al. 2014). Relapse to smoking is particularly rapid among those with schizophrenia and bipolar disorder (SBD) following discontinuation of pharmacotherapy (Evins et al. 2007) and improved with maintenance treatment (Evins et al. 2014).

The high prevalence of tobacco smoking among those with psychiatric illness (Cook et al. 2014) may be in part due to failure to offer cessation treatment at the same rate as those in the general population (Druss et al. 2001; Huang et al. 2014). For those with SBD who receive cessation treatment, it is unknown whether higher smoking rates are due in part to lower initial abstinence rates, higher relapse rates or both and whether these are modified by known risk factors such as severity of nicotine dependence. Because smokers with SBD have been excluded from large smoking cessation trials, opportunities for direct comparisons of relapse rates by psychiatric diagnosis, controlling for factors associated with both SBD and abstinence such as severity of dependence, have been unavailable.

We sought to compare the effect of maintenance pharmacotherapy on sustained abstinence rates in smokers with SBD with those without psychiatric illness. To do so, we conducted a pooled analysis from two

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randomized, double-blind, placebo-controlled, relapse-prevention trials that employed similar study designs and were conducted in adult smokers with SBD and those from a general population sample that excluded smokers with psychiatric illness (Evins et al. 2014; Tonstad et al. 2006). In both trials, initial abstinence rates with varenicline and behavioral therapy were substantial, and those assigned to maintenance varenicline had higher abstinence rates during maintenance treatment than those assigned to placebo. Our hypothesis was that, after controlling for factors associated with both smoking and SBD, maintenance treatment with varenicline would normalize relapse rates for those with SBD, while a large effect of SBD diagnosis on relapse and time to first lapse would be observed in those assigned to placebo.

2. Methods

2.1. Description of data sets

The data for this analysis were collected in two randomized controlled trials that tested the efficacy of maintenance varenicline for smoking relapse prevention in smokers with SBD (Evins et al. 2014) and without psychiatric illness (Tonstad et al. 2006) who attained initial abstinence during a 12-week, open-label varenicline treatment phase. Participants with SBD were enrolled from community mental health centers in six US states (Evins et al. 2014) and those without psychiatric illness were enrolled from six US and 18 international (Canada, Czech Republic, Denmark, Norway, Sweden, and UK) medical clinics (Tonstad et al. 2006). Both studies provided weekly behavioral treatment and open-label varenicline, 0.5 mg per day for 3 days, 0.5 mg twice a day for 4 days, then 1.0 mg twice a day for 11 weeks. Participants with 14-day (Evins et al. 2014) or 7-day (Tonstad et al. 2006) point prevalence abstinence at week 12 were randomized to receive varenicline (1.0 mg twice a day) or identical placebo and a tapering schedule of behavioral support for abstinence. Treatment was continued for 40 weeks in those with SBD (Evins et al. 2014) and for 12 weeks in those without psychiatric illness (Tonstad et al. 2006). Participants were then followed off treatment for 12 and 28 weeks post-treatment, respectively.

To facilitate direct comparison of abstinence rates between the study populations, we censored data at week 24, the end of 12-week maintenance treatment for those without SBD, and at week 25, the nearest comparable visit, for those with SBD. A 7-day window was allowed to complete this visit, referred to in this report as week 24. Four-week continuous abstinence rates after 12 weeks of maintenance therapy was defined as self-report of not smoking in the prior 4 weeks and expired carbon monoxide (CO) concentration <9 ppm at the week-24 visit. For both studies, abstinence status was coded as missing if self-reported smoking status was missing and associated expired CO concentration data was either also missing or was <9 ppm. Missing smoking status was coded as abstinent if subsequent visits indicated abstinence since the last visit. Eighty-seven individuals with SBD were randomized to maintenance varenicline ($n = 40$) or identical placebo ($n = 47$), and 1206 individuals without psychiatric illness were randomized to varenicline ($n = 602$) or placebo ($n = 604$).

2.2. Data analysis

To assess the impact of missing data on abstinence rates, a multiple imputation process was applied to each of the source datasets separately, so as not to assume similar processes underlying the missing data patterns in the populations. Variables in the imputation models included treatment assignment, site, gender, race (Caucasian, other), age, severity of dependence (Fagerstrom Test for Nicotine Dependence (FTND) total score(Heatherton et al. 1991), cigarettes smoked per day (lifetime), age at initiation of regular smoking, prior cessation attempts (log-transformed), duration of longest previous abstinence, all observed CO measurements and smoking status reports between randomization and missing data point, as well as variables summarizing the open phase, including number of abstinent weeks, number of lapses, and minimum and maximum (log-transformed) observed CO. For imputation models of those with SBD, we included psychiatric symptom severity as assessed with the Brief Psychiatric Rating Scale (Overall and Gorham 1962) total score, hedonic capacity as assessed with the Snaith-Hamilton Pleasure Scale (Snaith et al. 1995), and physical and mental health components of the SF-12 (Salyers et al. 2000).

We appended the imputed datasets from both studies, analyzed each combined imputed dataset with a generalized linear mixed (GLIMMIX) model for logistic binary outcomes, and combined the results using Rubin's method. (Rubin 1976, 2008) The GLIMMIX model of 4-week continuous abstinence rates at week 24 included fixed predictors of diagnosis (SBD, no SBD), treatment (varenicline, placebo), diagnosis by treatment interaction, baseline total FTND, and race, and site as a random predictor. We used the imputed data set of point-prevalence abstinence at all study visits to fit a longitudinal logistic regression model of point-prevalence abstinence with random intercepts and coefficients, adjusting for linear effects of gender, race, age, and severity of nicotine dependence, to test if effect of time on abstinence differed between diagnostic groups or treatment.

Time to first lapse was defined as the interval from randomization to the first study visit at which a participant reported smoking. Participants randomized without 7-day point-prevalence abstinence at week 12 ($n = 2$ SBD, $n = 7$ no-SBD) and those who dropped out immediately after randomization ($n = 1$ SBD, $n = 11$ no-SBD) were excluded, resulting in a sample size of $n = 1272$ for the survival analyses. For participants who did not smoke prior to the week-24 visit, time to first lapse was censored at week-24, corresponding to the end of active treatment in those without SBD. Time to first lapse was analyzed using a nonparametric analysis of interval-censored data. Because fewer than half of participants lapsed by week-24 (832 participants (65%) on varenicline: 24% with SBD, 24% without SBD; on placebo: 72% with SBD, 43% without SBD), we present the 25th percentile (Q1) of days to first lapse rather than median days to first lapse.

There were missing data due to drop out: 5.0%, 7.0%, 12.8%, and 13.7% in the SBD and general population groups treated with varenicline and placebo, respectively. Additional statistical methods and sensitivity analyses with alternate approaches to handling missing data, a multiple imputation model without baseline covariates, and a matched sample analysis to address concerns about baseline differences between diagnostic groups are included in Supplementary Materials. Analyses were performed using SAS 9.4.

3. Results

Of 202 smokers with SBD and 1927 smokers without psychiatric illness who entered 12-week open-label treatment trials of varenicline and behavioral therapy for smoking cessation, 87 participants (43%) with SBD and 1206 participants (63%) without SBD achieved 14- and 7-day point prevalence abstinence, respectively, at week 12, and were randomly assigned to continue varenicline or identical placebo. Compared to those without SBD, randomized participants with SBD were older, more likely to be male, more racially diverse, more severely nicotine dependent, more likely to have tried NRT, and to have smoked more cigarettes per day on average during their lifetime (Table 1). Randomized participants did not differ by diagnostic group on expired CO, cigarettes smoked per day in recent past, age at initiation of smoking, years smoking, or serious quit attempts in the prior year.

3.1. Abstinence outcomes

Continuous abstinence rates, time to first lapse, and retention rates are presented in Table 2. There was a main effect of treatment; those assigned to varenicline had increased odds of abstinence at week 24 (OR: 2.87, 95%CI: 2.19–3.77; $t_{1202} = 7.62$, $p < 0.001$). There was also a

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Table 1
Baseline characteristics of participants entering smoking cessation and maintenance treatment phases in trials of those with and without SBD.

	Open-label cessation phase					Randomized maintenance phase				
	Participants with SBD, $n = 202$		Participants without SBD, $n = 1927$			Participants with SBD, $n = 87$		Participants without SBD, $n = 1206$		
Demographics‡										
Age, y	47.6	(10.0)	44.2	(10.7)	***	48.3	(10.3)	45.3	(10.4)	**
Sex, % female	39.6		51.2		**	36.8		50.7		*
White, %	74.3		96.2		***	73.6		96.8		***
Black, %	17.3		1.8		***	17.2		1.6		***
Smoking history										
Expired CO, ppm†¥	23.1	(14.9)	22.2	(10.6)		21.4	(14.1)	21.7	(10.3)	
Cigarettes per day (recent)† ¥	22.8	(12.1)	21.6	(8.3)		20.4	(12.0)	20.7	(7.4)	
Cigarettes per day (lifetime)†	25.8	(14.2)	19.4	(7.1)	***	23.1	(9.5)	19	(6.4)	***
FTND total score	6.1	(1.8)	5.6	(2.0)	***	5.9	(1.8)	5.4	(2.0)	*
FTND score > =6, %	63.2		52.8		**	58.6		48.5		
Age started smoking, y	17.6	(5.7)	16.2	(3.7)	**	17.2	(5.4)	16.3	(3.7)	
Years of smoking	27.9	(12.0)	27.2	(10.7)		29	(12.3)	28.1	(10.4)	
Quitting history										
Serious quit attempt, prior year, %	41.6		38.3			43.7		39.3		
Tried nicotine gum to quit, %	47.0		27.8		***	46.0		29.0		***
Tried nicotine patch to quit, %	58.4		42.7		***	57.5		44.3		*
Tried other medication to quit, %	35.6		35.5			37.9		38.0		
Randomized, %	43.1		62.6		***	~		~		

Data presented as mean (SD) unless otherwise noted where * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ based on chi-square tests for percentages or 2-sample t-tests with unequal variances (pooled variance for age and FTND total) for continuous measures.
FTND = Fagerstrom Test for Nicotine Dependence (scale range: 0–10).
† log-transformed for analysis.
¥ "Recently" refers to past week for those with SBD, and to past month for participants without SBD.
‡ Data based on serious quit attempts (>24 h) for no-SBD group and on any quit attempt plus a lifetime history of at least one serious quit attempt for SBD group due to protocol differences.

main effect of diagnosis; those with SBD had lower odds of abstinence than those without psychiatric illness (OR: 0.27, 95%CI: 0.13, 0.56; $t_{1190} = -3.51$, $p < 0.001$). There was a significant treatment by diagnosis interaction such that there was no difference in abstinence rates by diagnosis among those assigned to varenicline, ($n = 40$ SBD, $n = 602$ no SBD) (87.2 ± 0.8% SBD vs. 81.9 ± 0.2% no psychiatric illness, OR: 1.68, 95%CI: 0.53, 5.32, $p = 0.38$), but for those assigned to placebo, the week-24 abstinence rate for those with SBD was less than half that for those without psychiatric illness ($n = 47$ SBD, $n = 604$ no SBD) (29.4 ± 1.1% vs. 61.8 ± 0.4%, OR: 0.26, 95% CI: 0.13, 0.52, $p < 0.001$).

In the combined sample, female sex (OR: 0.75, 95%CI: 0.58, 0.97; $t_{1188} = -2.16$, $p = 0.031$) and greater nicotine dependence severity (OR: 0.88, 95%CI: 0.82, 0.94; $t_{1184} = -3.86$, $p < 0.001$) were associated with lower odds of abstinence at week-24. Race and age had no effect on abstinence. Alternate approaches to missing data, a model without covariates, and a matched case analysis yielded similar parameter estimates and conclusions (see Supplementary materials).

There was no effect of diagnosis in the effect of time on point-prevalence abstinence among those assigned to maintenance varenicline (OR: 0.91, 95%CI: 0.78–1.06 vs. OR: 0.92, 95%CI: 0.84–1.00, respectively, $t_{5000.4} = 0.13$, $p = 0.897$). However the effect of time on abstinence rates was significant among those assigned to placebo; those with SBD on placebo had lower odds of remaining abstinent from week to week (OR: 0.74, 95%CI: 0.66–0.84, vs. OR: 0.85, 95%CI: 0.78–0.92, respectively, $t_{2455.5} = 2.54$, $p = 0.011$; Fig. 1). Female sex and greater nicotine dependence severity were associated with lower odds of abstinence from week to week (OR: 0.97, 95%CI: 0.94–1.00; $t_{4040.3} = -2.16$, $p = 0.031$), and (OR: 0.99.95%CI: 0.98–0.99; $t_{4461.4} = -3.44$, $p < 0.001$), respectively; race and age had no effect on weekly abstinence rates. See Fig. 1.

3.2. Time to first lapse

Time to first lapse was shortest in participants with SBD on placebo (Q1 = 12 days, 95% CI: 4–16), followed by those without SBD on placebo (Q1 = 17 days, 95% CI: 17–29), then participants without SBD on varenicline (Q1 = 88, 95% CI: 58–91), and longest in those with SBD on varenicline (Q1 > 95 days and 95% CI: non-est.). ($X^2_{3df} = 96.99$, $p < 0.0001$; all pairwise comparisons $p < 0.001$) Fig. 2.

4. Discussion

This is the first comparison of the effect of maintenance smoking cessation pharmacotherapy on relapse course in recently abstinent smokers with and without SBD to our knowledge. Among those assigned to placebo, those with SBD were more likely to relapse and lapsed sooner than smokers without psychiatric illness. Maintenance pharmacotherapy reversed this effect. Among those on maintenance

Table 2
Abstinence outcomes by diagnosis and treatment, using multiple imputation for missing data for 4-week continuous abstinence after 12 weeks of maintenance therapy with varenicline or placebo.

Outcome	Schizophrenia-bipolar disorder		No psychiatric illness	
	Varenicline $n = 40$	Placebo $n = 47$	Varenicline $n = 602$	Placebo $n = 604$
4-Week Continuous Abstinence at Week 24, %	87.2 ± 0.8	29.4 ± 1.1	81.9 ± 0.2	61.8 ± 0.4
12-Week Continuous Abstinence at Week 24, %	74.7 ± 0.9	27.1 ± 0.9	73.4 ± 0.2	55.2 ± 0.3
Time to first lapse, Q1	> 95 days	12 days	88 days	17 days
Dropped out before week 24, %	5.0	12.8	6.1	12.6

Q1 indicates first quartile.

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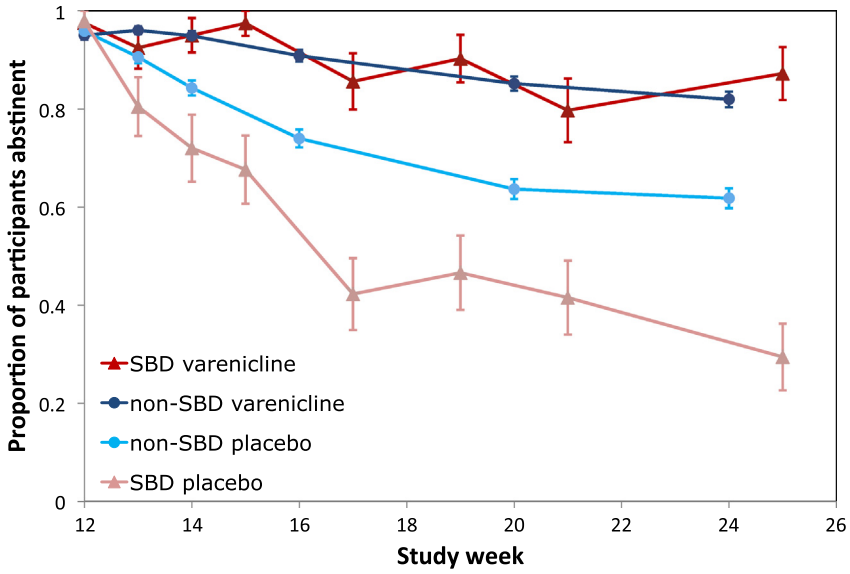

Fig. 1. Point prevalence abstinence rates at each study visit in recently abstinent smokers with or without schizophrenia or bipolar disorder during maintenance treatment with varenicline or placebo. Error bars represent standard deviations around the estimated mean proportion of abstinent participants from 50 imputed data sets.

varenicline, the 6-month abstinence rates and time to first lapse was no different in those with SBD than for those without psychiatric illness. This suggests that maintenance pharmacotherapy may be a useful tool in the effort to reduce the disparity in smoking-related morbidity and mortality in those with SBD (Everett et al. 2008; Lutterman et al. 2003).

Relapse is a central problem in addiction treatment in general and in smoking cessation treatment in particular. Despite promising end-of-treatment abstinence rates with 8–12 week courses of first-line pharmacotherapies (Fiore et al. 2008), continuous abstinence rates at one year and beyond are low (Etter and Stapleton 2006; Gilpin et al. 1997; Hughes et al. 2008). Maintenance treatment that prolongs initial abstinence may yield higher sustained abstinence rates, with attendant health and longevity benefits. A recent meta-analysis of relapse-prevention interventions did not support maintenance treatment for relapse prevention among recently abstinent smokers in the general population (Hajek et al. 2013); the single positive trial of varenicline for relapse prevention (Tonstad et al. 2006), was insufficient to support conclusions about efficacy of maintenance varenicline for relapse prevention.

We observed that people with schizophrenia and bipolar disorder were more likely to relapse to smoking without maintenance varenicline treatment and no more likely to relapse when provided maintenance varenicline. While standard combination pharmacotherapy and behavioral treatments are effective for initial abstinence in smokers with schizophrenia spectrum and bipolar disorders (Chengappa et al. 2014; Evins et al. 2007; Evins et al. 2005a; George et al. 2008; George et al. 2002; Williams et al. 2012) smoking rates are not declining among those with psychiatric illness (Cook et al. 2014). The particularly rapid relapse observed following discontinuation of a standard course of pharmacotherapy for those with SBD could be a significant contributing factor to this population level effect (Chengappa et al. 2014; Evins et al. 2007; Evins et al. 2014). Mechanisms by which maintenance pharmacotherapy may be differentially helpful for

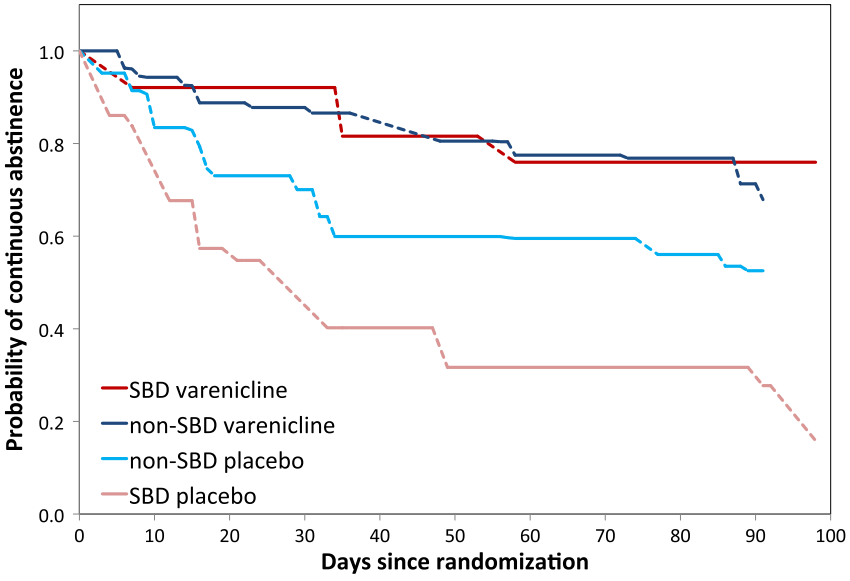

Fig. 2. Duration of continuous abstinence, censored at first lapse, in recently abstinent smokers with and without schizophrenia or bipolar disorder (SBD) assigned to varenicline or placebo. Dotted segments in each line are plotted across intervals for which the survival estimates are not defined.

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maintenance of abstinence in smokers with schizophrenia include positive effect of nicotinic agonists and negative effects of abstinence and nicotinic antagonists on schizophrenia-related cognitive deficits, (Barr et al. 2008a; Culhane et al. 2008; Evins et al. 2005b; Hong et al. 2011; Roh et al. 2014; Shim et al. 2012) but see (Smith et al. 2016); reward responsiveness, (Barr et al. 2008b; MacKillop and Tidey 2011; McClure et al. 2013; Spring et al. 2003; Tidey et al. 2014; Tidey et al. 2013) and urges to smoke (Smith et al. 2016).

In controlled trials, varenicline has been consistently reported to be effective and well tolerated in individuals with and without psychiatric illness (Anthenelli et al. 2016; Anthenelli et al. 2013; Chengappa et al. 2014; Evins et al. 2014; Kaduri et al. 2015; Williams et al. 2012). In up to one year of dosing, maintenance treatment with varenicline and counseling has been reported to be effective for sustained abstinence (Evins et al. 2014; Tonstad et al. 2006) and a cost-effective alternative to a 12-week treatment course. (Knight et al. 2012; von Wartburg et al. 2014). The demonstrated safety, tolerability, efficacy, and cost-effectiveness of maintenance varenicline make it an attractive option to improve long-term abstinence for smokers with and without SBD. Reduced relapse rates with maintenance treatment for those with SBD who attain early abstinence could narrow the gap in smoking prevalence that has been associated with a lifespan disparity of 28 years for those with schizophrenia (Olfson et al. 2015).

5. Limitations

The comparison of time to first lapse by diagnosis in the placebo arm should be interpreted in light of the limitations of a pooled analysis of separate trials, though the trials were similar in design and execution. Abstinence was assessed at two additional time points between post-randomization weeks 2–9 in those with SBD. Fewer assessments in the trial in those without psychiatric illness may have resulted in lower precision in the estimate of time to relapse, with risk of a slight relative overestimation of the time to first lapse in post-randomization weeks 2–9 in this group. For this reason, the finding that among those assigned to placebo those with SBD had a shorter time to first lapse than those without SBD should be interpreted with caution. Among those assigned to varenicline, the more frequent assessments between weeks 2 and 9 should have little effect, as their estimated time to relapse is much longer. The final study visit included for those with SBD was one-week later than the nearest corresponding study visit for those without SBD, such that more smokers with SBD could have lapsed during that week. As the time to lapse curves were fairly level at that point, the impact was likely minimal.

Those with SBD were offered a higher-intensity behavioral intervention, 1-h group cognitive-behavioral therapy (CBT) at each visit, while those without psychiatric illness were offered a 10-min individual smoking cessation intervention at each visit. Relapse was rapid and common in those with SBD assigned to maintenance placebo despite more intense behavioral treatment, suggesting the impact of differential behavioral therapy intensity may have reduced the magnitude of the observed interaction effect of treatment and diagnosis on abstinence outcomes. If an interaction between varenicline and behavioral therapy is present in those with SBD as has been suggested (Evins et al. 2014), differential intensities of behavioral therapy by diagnosis could have accentuated the treatment by diagnosis interaction. Finally, the abstinence requirement for randomization differed, with 7-day point-prevalence abstinence required for those without psychiatric illness and 14-days abstinence required for those with SBD, which could have yielded more serious quitters in the relapse prevention phase in the SBD trial that would be expected to result in lower relapse rates in those with SBD that was not observed in the placebo group.

Finally, there was missing data, but, perhaps because the amount of missing data was relatively small, the findings were robust across four analytic approaches to missing data and an analysis using a sample matched on several baseline characteristics that differed in the full sample (i.e., age, gender, nicotine dependence severity, previous smoking cessation medication use, and past year quit attempt).

6. Conclusion

Without maintenance pharmacotherapy, the rate of relapse to smoking for those with SBD was significantly higher and more rapid than for those without psychiatric illness, but with maintenance pharmacotherapy there was no effect of SBD diagnosis on the rate or timing of relapse.

Given the mounting evidence for safety of varenicline in those with and without SBD, and the known large detrimental health effects of continued smoking, maintenance varenicline should be considered as a tool to helping smokers with and without SBD to attain sustained tobacco abstinence. Improved long-term tobacco abstinence rates could have substantial public health impact for those with serious mental illness, as tobacco smoking is estimated to account for two-thirds of the mortality disparity for this group (Tam et al. 2016). Further research is needed to identify the mechanism by which varenicline may reduce the disparity in smoking relapse rates between those with and without SBD.

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Author contributions

Drs. Evins, S. Hoeppner and Schoenfeld designed the study and wrote the statistical analysis plan. Drs. Evins, Culhane Maravic, and Cieslak managed the literature searches and analyses. Dr. S. Hoeppner undertook the statistical analysis with critical input from Drs. B Hoeppner and Schoenfeld. Dr. S. Hoeppner wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.schres.2016.11.018.

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