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

A. Eden Evins [a,*,1], Susanne S. Hoeppner [a,1], David A. Schoenfeld [b], Bettina B. Hoeppner [a], Corinne Cather [a], Gladys N. Pachas [a], Kristina M. Cieslak [a], Melissa Culhane Maravic [a]

[a] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States
[b] Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States

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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

* Corresponding author at: Massachusetts General Hospital Center for Addiction Medicine, 60 Staniford St., Boston, MA 02114, United States.
E-mail address: a_eden_evins@hms.harvard.edu (A.E. Evins).
[1] Contributed equally.

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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