

## Maintenance Treatment with Varenicline for Smoking Cessation in Patients with Schizophrenia and Bipolar Disorder: A Randomized Clinical Trial

### BACKGROUND:

- Fifty-three percent of US adult with serious mental illness smoke tobacco
- Small trials have shown that pharmacologic cessation aids increase initial abstinence rates over behavioral treatment alone for smokers with schizophrenia and schizoaffective disorder and that abstinence rates decrease after discontinuing pharmacotherapy
- This suggests that behavioral therapy alone is ineffective for smoking cessation in this population and that long-term pharmacotherapy may be necessary

### OBJECTIVE:

- To determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment.

### METHODS:

- **Design:** Randomized, double-blind, placebo-controlled, parallel-group clinical trial. Therapy duration: 52 weeks
- **Inclusion criteria:**
  - **Phase I:** outpatient, 18-70 yo, diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder who reported smoking 10 or more cigarettes per day for at least the prior year, had expired carbon dioxide levels higher than 9 ppm at screening, expressed willingness to take varenicline, agreed to attempt smoking cessation by setting a quit date within 4 weeks of enrollment, and were taking a stable clinically determined dose of antipsychotic (schizophrenia spectrum) or mood stabilizing (bipolar disorder) medication for 30 days or more before enrollment
  - **Phase II:** Patients in the open phase who met criteria for biochemically verified, 7-day, point-prevalence abstinence at weeks 11 and 12 were considered to be continually abstinent for at least 14 days and were randomized to relapse prevention intervention
- **Exclusion criteria:**
  - Current suicidal or homicidal ideation, hospitalization for suicidality in the prior 12 months, other active substance use disorder, or major depressive episode in the prior 6 months.
- **Primary outcome measure:** 7-day point-prevalence abstinence rate at week 52
- **Secondary outcome measures:**
  - Continuous abstinence rates during the randomized and follow-up phases
  - Point-prevalence abstinence rates at week 64
  - Median time to first smoking relapse
  - Effect of varenicline on psychiatric symptoms (Calgary Depression Scale for Schizophrenia, Brief Psychiatric Rating Scale, Schedule for Assessment of Negative Symptoms), nicotine withdrawal symptoms (Wisconsin Smoking Withdrawal Scale), health-related quality of life (SF-12), body mass index, and adverse events

## RESULTS:

- **Primary outcome measure:** 24 of the 40 patients (60%) in the varenicline group achieved biochemically verified, 7-day point-prevalence abstinence at week 52 vs 9 of 47 patients (19%) in the placebo group (OR 6.2, 95% CI 2.2-19.2;  $p < 0.001$ )
- **Secondary outcome measures:**
  - Continuous abstinence rates during the randomized and follow-up phases:
    - From weeks 12-52: 18 of 40 (45%) achieved continuous abstinence in the varenicline group vs 7 of 47 (15%) in the placebo group (OR 4.6; 95% CI 1.5-15.7;  $p=0.004$ )
    - After treatment discontinuation from weeks 12-64, 16 of 40 (40%) of patients in varenicline group vs 5 of 47 patients (11%) in placebo group were continuously abstinent (OR 5.2; 95% CI 1.6-20.4;  $p=0.003$ )
    - By week 76, 12 of 40 patients (30%) in varenicline group vs 5 of 47 in placebo group had been continuously abstinent since randomization at week 12 (for a total of 16 months) (OR 3.4; 95% CI 1.02-13.5;  $p=0.03$ )
  - Point-prevalence abstinence rates at week 64: 18 of the 40 (45%) patients in the varenicline group vs 6 of 47 patients (13%) in the placebo group achieved 7-day point-prevalence abstinence at week 64 (OR 5.1, 95% CI 1.7-18.0;  $p=0.002$ )
  - Median time to first smoking relapse: Median time to relapse 358 days for those in the varenicline group and 35 days for those in the placebo group ( $p < 0.001$ )
  - No effect of varenicline on severity of psychiatric symptoms, on self-report of overall health, BMI, or on nicotine withdrawal symptoms
- **Authors' conclusion:** In smokers with serious mental illness who attain initial abstinence with a standard 12-week course of varenicline and cognitive behavioral therapy (CBT), 40 additional weeks of maintenance treatment with varenicline plus CBT resulted in improved prolonged abstinence rates compared with placebo plus CBT. Maintenance treatment may reduce the high prevalence of tobacco dependence and reduce the heavy burden of smoking-related morbidity and mortality in those with serious mental illness.

## STRENGTHS:

- Similar characteristics at baseline
- Limited potential for bias despite some conflicts of interest
- Study design
- Measures to limit variability in assessments between sites
- Multicenter trial, easier to extrapolate to a broad population

## LIMITATIONS:

- Small sample size ( $n=87$ )
- Disproportionate number of patients with schizophrenia vs bipolar disorder
- Potential for unblinding

- Power only reported for the primary outcome
- Non-smoking secondary outcomes not explicitly discussed (no P values)
- No specific analysis or discussion for patients with bipolar disorder
- High drop-out rate

#### CONCLUSION:

- Based on the high prevalence of tobacco use in patients with serious mental illness and the high rate of relapse after a cessation attempt, long-term pharmacologic treatment is necessary in this patient population (as long as the benefits outweigh the risks of therapy).
- Future Research:
  - Larger sample size
  - Separate patients by diagnosis
  - Longer duration of treatment
  - Compare pharmacologic smoking cessation treatments

**Reference:** Evins AE, Cather C, Pratt SA, Pachas GN, Hoepfner SS, Goff DC, et al. Maintenance Treatment with Varenicline for Smoking Cessation in Patients with Schizophrenia and Bipolar Disorder: A Randomized Clinical Trial. JAMA. 2014; 311(2): 145-154.

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