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EFFICACY AND SAFETY OF VARENICLINE FOR SMOKING CESSATION IN SCHIZOPHRENIA: A DETAILED REVIEW

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ABSTRACT

Individuals with schizophrenia smoke at higher rates (58%– 88%) than the general population, and have difficulty quitting. Smoking is a major public health problem and is a leading cause of preventable death. Despite the high prevalence of smoking among people with schizophrenia, there are few effective treatments for smoking cessation in this population. Varenicline has not been studied extensively in patients with mental illnesses, particularly in those with schizophrenia, a population with an exceptionally high prevalence of nicotine addiction. Although case reports and small case series initially suggested that varenicline may be associated with increased risk of neuropsychiatric adverse effects in psychiatric populations, subsequent studies from case reports and case series to larger clinical trials have demonstrated that the medication can be safely administered to aid schizophrenia patients with smoking cessation with minimal adverse events. Thus, further research is needed. The objective of this study is to evaluate the efficacy of varenicline for smoking cessation among individuals with schizophrenia. Among the 828 surveyed articles, only four randomized controlled trials (RCTs) with a total of 239 participants met the criteria for meta-analysis. The results of the meta-analysis revealed that compared to placebo, varenicline treatment significantly decreased the number of cigarettes consumed per day [standardized mean difference (SMD) (95% confidence interval (CI)) = 0.89 (0.57–1.22)] and the expired carbon monoxide levels [SMD (95% CI) = 0.50 (0.06–0.94)] in patients with schizophrenia. Despite the small sample size of studies included in the meta-analysis, our findings suggest that varenicline is an effective and safe drug to assist smoking cessation among patients with schizophrenia. Further well-designed, large-scale randomized controlled trials are needed to validate these results.

KEYWORDS: Varenicline, schizophrenia, randomized controlled trials, meta-analysis, standardized mean difference.

INTRODUCTION

Varenicline, an FDA-approved drug, has been shown to effectively aid non-psychotic smokers in quitting smoking. It acts as a high affinity partial nicotinic agonist at the α2β4 nicotinic receptor and a full agonist at neuronal α7 nicotinic receptor. Schizophrenic patients have a high rate of cigarette smoking and cognitive deficits, which may be linked to defects in their nicotinic receptors, particularly a reduction in the α7 neuronal nicotinic receptor numbers. Smoking or nicotine administration may transiently improve psychophysiological measures related to sensory gating deficits and cognitive performance in schizophrenia.[1] A preliminary open study of varenicline's effects in schizophrenics indicated cognitive improvement and no negative psychiatric effects. However, early reports suggested that varenicline might have psychiatric side-effects, including increases in depression, suicide, or psychosis in vulnerable patients.[2] A double-blind placebo-controlled study was conducted to investigate the effects of standard clinically used doses of varenicline on smoking, cognition, psychopathology, and side effects in schizophrenic patients who smoke cigarettes. The study hypothesized that varenicline would improve cognition and reduce smoking in patients with schizophrenia.[3] Two other double-blind studies were published on the effects of varenicline on cognition and symptoms in schizophrenia, which are compared in the discussion section. People with schizophrenia have a significantly higher prevalence of smoking, smoke more cigarettes per day, self-administer higher doses of nicotine per cigarette, and have a higher mortality rate from smoking-related diseases than those in the general population. Nicotine dependence treatment is often

overlooked for smokers with mental illness, making tobacco smoking a modifiable risk factor that requires attention. Varenicline is a partial alpha4beta2 nicotine acetylcholine receptor (NAChR) agonist and full α7NAChR agonist that is effective and cost-effective for smoking cessation.[4] Although varenicline has been well tolerated with respect to psychiatric adverse events in all controlled trials published to date, post-marketing case reports of psychiatric adverse events in smokers taking varenicline prompted an FDA-mandated warning of neuropsychiatric symptoms to be included in prescribing information for varenicline. Controlled trials to date have excluded smokers with current psychiatric illness, but uncontrolled case reports and larger retrospective studies have reported generally good tolerability of varenicline with respect to psychiatric symptoms in stable, treated outpatients with schizophrenia and depression. The exclusion of smokers with major psychiatric illnesses from large, prospective trials of varenicline may have prevented the detection of common psychiatric adverse events in this vulnerable population. Despite limited safety data for smokers with schizophrenia, many formularies across the United States are restricting access to varenicline for these individuals.

To address these concerns, we conducted an interim analysis of a 12-week, open-label trial of varenicline and weekly group cognitive behavioral therapy (CBT) in stable outpatient smokers with schizophrenia. Our study prospectively evaluated psychiatric symptoms, adverse events, and smoking outcomes during treatment with varenicline and CBT.[5]

HISTORICAL BACKGROUND

Varenicline, sold under the brand name Chantix in the United States and Champix in other parts of the world, is a medication used to help people quit smoking. Here is some historical background data on varenicline.[6]

Varenicline was first synthesized in the late 1990s by scientists at Pfizer, Inc. in Groton, Connecticut, as part of a research program to develop new smoking cessation treatments. The compound was identified as a partial agonist of the α4β2 nicotinic acetylcholine receptor, which is involved in nicotine addiction.

After preclinical studies showed promising results, varenicline entered clinical trials in 2002.[7] The trials were conducted in several countries and involved more than 3,000 smokers. The results showed that varenicline was more effective than placebo in helping smokers quit and was generally well-tolerated.[8]

In 2006, varenicline was approved by the U.S. Food and Drug Administration (FDA) as a smoking cessation aid. It was the first new drug in this category to be approved in over a decade. The FDA granted varenicline a priority review designation, which allowed for a faster approval process.

Varenicline was subsequently approved in other countries, including Canada, the European Union, and Australia. In some countries, such as the United Kingdom, it is available on the National Health Service (NHS) as a prescription medication.[9]

Varenicline has been the subject of controversy over the years, with some studies and reports suggesting that it may be associated with an increased risk of psychiatric side effects, such as depression, suicidal ideation, and aggressive behaviour.[10] However, other studies have not found a significant link between varenicline and these side effects, and the FDA and other regulatory agencies continue to consider it a safe and effective treatment for smoking cessation.[11]

METHODOLOGY

"Varenicline for Smoking Cessation in Schizophrenia: Safety and Effectiveness in a 12-Week Open-Label Trial" by Gladys N. Pachas, MD,1,2 Corinne Cather, PhD,1,2 Sarah I. Pratt, PhD,3 Bettina Hoeppner, PhD,1,2 Johanna Nino, MD,1 Sara V. Carlini,1 Eric D. Achtyes, MD, MS,4 Harry Lando, PhD,5 Kim T. Mueser, PhD,6 Nancy A. Rigotti, MD,1,2 Donald C. Goff, MD,1,2 and A. Eden Evins, MD, MPH1,2 the method is done by during the 12-week open-label trial.[12] a combination of varenicline and weekly group cognitive behavioural therapy was used to help smoking cessation in stable outpatient smokers with schizophrenia.[13] The trial was conducted as part of a larger 40-week double-blind, placebo-controlled relapse-prevention trial from April 2008 to July 2010. The trial was conducted at three different locations - Massachusetts General Hospital, Dartmouth Psychiatric Research Centre, and Michigan State University, in collaboration with local mental health centres.[14] The results of the relapse prevention phase of the trial will be published elsewhere. The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki, FDA guidelines, and the International Conference on Harmonization Good Clinical Practices Guidelines.[15] The study was approved by human subjects review boards at each site, and all participants provided written informed consent before the study began.[16]

Participants

The study enrolled women and men aged between 18 and 70 years who had a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder and smoked 10 or more cigarettes per day. Participants had to be clinically stable on a consistent dose of antipsychotic medication for at least one month and expressed a desire to quit smoking.[17] Additionally, their expired carbon monoxide levels needed to be greater than 9 ppm. Exclusion criteria for the study included having an unstable medical illness, diagnosis of dementia or substance use disorder other than nicotine or caffeine in the prior 6 months, or being hospitalized for suicidal ideation within the last 12 months.[18] The inclusion and exclusion criteria ensured that the study participants were

in good overall health and had the capacity to provide informed consent.[19]

Intervention

As part of a smoking cessation program designed for individuals with schizophrenia, participants received a unique intervention consisting of varenicline and manualized cognitive behavioural therapy.[20] Varenicline was administered at a dose of 0.5 mg once daily for 3 days, followed by 0.5 mg twice daily for 4 days, and then 1 mg twice daily for 11 weeks.[21]

The cognitive behavioural therapy sessions were based on the Freedom From Smoking program developed by the American Lung Association, but tailored specifically for individuals with schizophrenia. To assess the effects of varenicline on psychiatric symptoms and minimize the impact of nicotine withdrawal, participants were encouraged to set a quit date between weeks 4 and 5.[22] Psychiatric symptoms were monitored for one month prior to the quit date and for two months following the quit date to evaluate the impact of smoking abstinence or reduction on mental health.[23]

Assessments

The assessments conducted during the study were comprehensive and included multiple measures to evaluate smoking behaviour, nicotine dependence, medical history, and psychiatric symptoms. The unique aspects of these assessments included expired carbon monoxide, the Fagerstrom Test for Nicotine Dependence (FTND), laboratory assessments, and self-report of smoking behaviour.[24] Weekly assessments included the Wisconsin Smoking Withdrawal Scale (WSWS) to assess nicotine withdrawal symptoms and the Calgary Depression Scale for Schizophrenia (CDSS) to assess depressive symptoms. Adverse event inquiry was also conducted to monitor any potential side effects associated with varenicline.[25] Baseline and end-of-treatment assessments included clinician ratings of psychiatric symptoms using the Brief Psychiatric Rating Scale (BPRS) and the Schedule for the Assessment of Negative Symptoms (SANS). Participants who terminated the study early were also asked to complete an early termination assessment of safety and smoking outcomes.[26] At each cognitive-behavioural therapy group visit, 7-day point prevalence abstinence was defined as self-report of not smoking any cigarettes for the prior 7 days and having an expired carbon monoxide level of less than 9 ppm.[27] Continuous abstinence was defined as consecutive weeks of biochemically verified 7-day point prevalence abstinence. Overall, the assessments used in this study provided a comprehensive evaluation of smoking behaviour and nicotine dependence, as well as potential psychiatric symptoms and adverse events associated with varenicline use.[28]

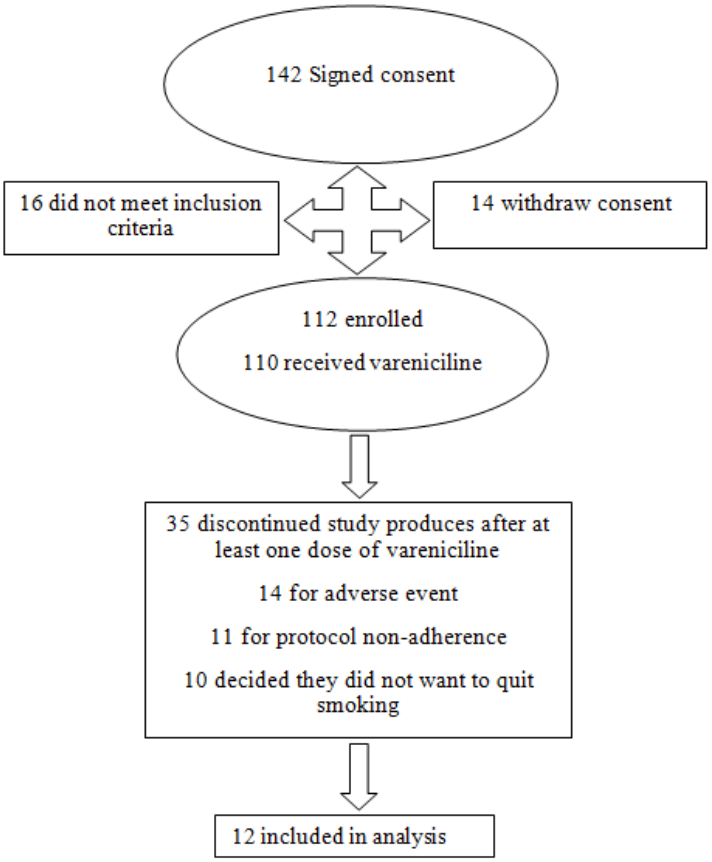
Analysis

The study enrolled 324 participants and conducted an interim analysis when one-third of the sample had been enrolled.[29] Paired t-tests were used to test for change over time in safety outcomes measured at baseline and end of treatment.[30] Repeated measures analyses were conducted to test for temporal trends in assessments performed weekly, with p-values adjusted using the false discovery rate method to address multiple significance testing.[31] Mixed effects models were used for normally distributed outcome variables, while generalized estimating equations were used for Poisson-distributed and binary outcome variables.[32] Retention biases were assessed using GEE analyses, and significant predictors of retention were included as covariates in all repeated measures analyses.[33] Baseline descriptors related to retention over time were weight and "age started smoking," with the latter included as a control variable in all analyses.[34] Safety outcomes were evaluated first in the entire cohort and then separately among those who dropped out versus those who were retained. For analyses of 2- and 4-week continuous abstinence rates at the end of treatment, participants who were not available to provide a carbon monoxide measurement at a given timepoint were considered to be smokers at that time point.[35]

REPORT OVERVIEW

Participants

In this study, out of 142 individuals who underwent the informed consent process, 16 were excluded as they did not meet the inclusion criteria, and 14 withdrew their consent before the study began. The remaining 112 participants were included in the analysis, with an average age of 47 years and 12 years of education.[36] They smoked over 20 cigarettes per day and had moderate to severe nicotine dependence, with an average FTND score of 6.1 (SD = 1.9). Of the 112 participants included, 37 (33%) discontinued treatment before week 12, with an average time point of discontinuation at 5.1 weeks (range 1 to 12 weeks), which was just after the quit date.[37] Among those who dropped out, 28 of 37 participants (77%) completed early termination assessments. It is important to note that despite the high dropout rate, the study was able to gather data from a significant number of participants, and the early termination assessments provide valuable insights into why some individuals may discontinue treatment.[38]



Psychiatric Symptoms and Nicotine Withdrawal Symptoms

The study findings reveal that there was no deterioration in ratings of psychiatric or nicotine withdrawal symptoms from baseline to week 12 or early termination.[39] However, significant improvements were observed in ratings of psychosis (BPRS psychosis subscale) and nicotine withdrawal symptoms, including urge to smoke, irritability, depression, concentration, and anxiety, from baseline to week 12 or early termination.[40]

Demonstrated that those who achieved 14-day point prevalence abstinence or terminated treatment early showed the same pattern of stable or improved psychiatric and withdrawal symptoms.[41] The repeated measures analyses showed that withdrawal symptoms decreased over time, while abstinence rates increased for most smoking outcomes and six out of nine clinical variables.[42] Linear trends were not significant for two subscales of the WSWS (depression, increased appetite) and for difficulty concentrating after correction for multiple tests. Age started smoking was used only as a covariate to statistically control for retention biases, but it was also found to be significantly related to urge to smoke and the total WSWS score.[43] The data indicate that 7-day point prevalence abstinence rates increased progressively over the course of the 12-week trial, and symptoms are unlikely to have worsened early during treatment and then recovered by week 12.[44]

Table 1: Demographics and Smoking History and Psychiatric and Nicotine withdrawal Rating.

	Baseline	Endpoint	t	
Age	47.2 (10) years	-	-	
Sex	44 (39.3%)female	-	-	
Education	12.2(2.8)years	-	-	
Race		-	-	
African American	16(14.3%)	-	-	
Caucasian	84(75%)	-	-	
Other	12(10.7%)	-	-	
Material status				
Single	73(65%)	-	-	
Married	9(8%)	-	-	
Divorced	23(21%)	-	-	

Widowed	6 (5.4%)	-	-
Employment status			
Disabled	67(59.8%)	-	-
Unemployed	13 (11.6%)	-	-
Working Part time	4 (4.0%)	-	-
Working full time	6.1 (1.9)	-	-
FTND			
Age began daily smoking	17.5(5.8)years	-	-
Years of regular smoking	27.7 (11.2)	-	-
CigarettesPerday	25.2 (13.5)	-	-
BPRStotal	536 (14.6)	51.76 (14.0)	1.643
BPRSpsychosis	14.21(6.95)	12.87 (6.39)	2.815*
SANS total	39.92 (15.03)	40.92 (15.90)	-0.914
CDSS total	4.23(3.13)	3.65(3.99)	1.511
WSWS total	59.09(11.54)	50.77(12.90)	6.808*
WSWS-Urge to smoke	11.85(2.104)	8.2(4.02)	8.718*
WSWS-Irritability	5.62(2.45)	4.46(2.92)	4.392*
WSWS-Depression	6.61 (3.14)	5.8(2.99)	2.677*
WSWS-Increased Appetite	11.79(3.46)	11.88(3.56)	-0.245
WSWS-Difficulty Concentrating	5.86(2.58)	5.15(2.39)	3.529*
WSWS-Insomnia	8.52(3.66)	8.25(3.87)	0.706
WSWS-Anxiety	8.84(2.82)	7.04 (2.69)	6.194*
Weight(Ib)	202.59(44.35)	207.6(45.4)	-5.374*
	23.04(15.52)	9.03(12.74)	8.872*

Table 2: Parameter Estimates for Outcomes Measured Weekly Over 12 weeks.

Outcome variable	Intercept			Slope			Model
	Est.	SE	t or z	Est.	SE	t or z	
CO	1.22	0.33	3.7**	-0.03	0.01	-2.8**	Poisson
Abstinent for at least the prior 7 days	-3.54	0.60	2.54	0.34	0.03	12.7**	Binary
WSWS total	60.92	2.54	24.0**	-0.65	0.15	-4.3**	Normal
Urge to smoke subscale	12.39	0.66	18.77**	-0.29	0.04	-7.0**	Normal
Irritability subscale	5.24	0.44	11.9**	-0.06	0.03	-2.1*	Normal
Depression subscale	6.64	0.52	12.9**	-0.04	0.03	-1.2	Normal
Increased Appetite subscale	12.22	0.65	18.7**	0.01	0.04	0.2	Normal
Diff. Concentrating subscale	6.45	0.50	12.9**	-0.06	0.03	-2.0	Normal
Insomnia subscale	8.25	0.61	13.5**	-0.09	0.04	-2.4*	Normal
Anxiety subscale	8.67	0.52	16.7**	-0.10	0.03	-3.1**	Normal
CDSS total	3.53	0.20	17.9	-0.14	0.01	-9.5**	Poisson

Note. All models include "age started smoking" as a covariate, which was a statistically significant predictor of retention across 12 weeks. Est. = Parameter estimate; SE = standard error; CO = carbon monoxide; WSWS = Wisconsin smoking withdrawal Scale; CDSS = Calgary Depression Scale for Schizophrenia. *p<.05. **p<.01

Table 3: Treatment emergent adverse events.

	Weeks 1 – 4	Weeks 5 – 12
	Before quit date	After quit date
Excitement		
Mild	13 (12%)	10 (9%)
Moderate	1 (1%)	11 (10%)
Severe	2 (2%)	4 (4%)
Agitation		
Mild	9 (8%)	7 (6%)
Moderate	5 (4%)	11 (10%)
Severe	1 (1%)	4 (4%)
Anxiety		
Mild	11 (10%)	9 (8%)

Moderate	11 (10%)	10 (9%)
Severe	2 (2%)	9 (8%)
Insomnia		
Mild	21(18%)	16 (14%)
Moderate	7(6%)	9 (8%)
Severe	1 (1%)	7 (6%)
Vomiting		
Mild	11 (10%)	12 (11%)
Moderate	5 (4%)	7 (6%)
Severe	2 (2%)	3(3%)
Tachycardia		
Mild	9 (8%)	9 (8%)
Moderate	0	8 (7%)
Severe	0	0

Contraindication

Prior to the designated quit date, a one-month lead-in period was implemented for administering Varenicline in order to evaluate any potential adverse effects on psychiatric symptoms.[45] This allowed for distinguishing between the confounding effects of nicotine withdrawal syndrome and the medication's impact on psychiatric symptom ratings and treatment-emergent adverse events.[46] The results of the study displays the psychiatric treatment-emergent adverse events during the four weeks before the target quit date and the eight weeks following it. Nausea was the most commonly reported adverse event, and it was generally described as mild or moderate and transient.[47] Among the three serious adverse events, all involved voluntary psychiatric hospitalizations. One participant who had not attained abstinence was discontinued from the study at week 6 due to dysphoric mood associated with exacerbation of chronic psychosocial stressors, which was deemed unrelated to study procedures. Another participant was hospitalized for dysphoric mood after seven weeks of abstinence.[48] Although the event was considered possibly related to study interventions, the participant remained on varenicline and abstinent throughout the hospitalization, ultimately completing the study upon discharge.[49] The third participant was discontinued from the study in week 3 and hospitalized for paranoia and suicidal ideation. The investigators believed that this was triggered by heavy cocaine use immediately before hospitalization, which could potentially have been related to study interventions. Furthermore, 12 participants experienced adverse events that led to treatment discontinuation, including nausea, anxiety, weight gain, depressed mood, paranoia, suicidal ideation, and substance use. The weight gain of around five pounds from baseline to the end of treatment was found to be significant.[50]

FUTURE

This innovative study sheds light on the potential effectiveness of a combination of varenicline and cognitive behavioural therapy in helping smokers with stable, treated schizophrenia and nicotine dependence quit smoking. The study found that over a 12-week period, participants who received this treatment demonstrated increased rates of abstinence from smoking and improvements in psychiatric symptoms such as withdrawal symptoms, depressive symptoms, and psychosis. These findings suggest that varenicline, a medication that has been shown to be highly effective for smoking cessation in the general population, may also be a promising option for smokers with schizophrenia and comorbid nicotine dependence, a population that is often underserved and faces significant mental health challenges.

While the study had certain limitations, such as the absence of a placebo control group and a relatively small sample size, it is still a valuable contribution to the field of smoking cessation research. The findings provide important insights into the potential benefits of combining medication and therapy in helping individuals with schizophrenia quit smoking, and highlight the need for further research to explore this approach more fully. By improving our understanding of the most effective strategies for smoking cessation in this vulnerable population, we may be able to reduce the significant burden of smoking-related health problems among people with schizophrenia and other mental health conditions.

CONCLUSION

Out of the 112 participants, 53 (47.3%) managed to sustain 2 or more consecutive weeks of biochemically verified continuous tobacco abstinence by week 12, while 38 (34%) achieved 4 or more consecutive weeks of continuous abstinence by the same time point. Interestingly, there was a significant temporal trend observed with a reduction in expired carbon monoxide and an increase in 7-day point prevalence abstinence over time (refer to Table 2). At baseline, the average expired carbon monoxide was 22.6 (14.2) ppm, which decreased to 9.0 (12.7) ppm by week 12 or early termination. Those who completed the full 12-week trial experienced a greater reduction in carbon monoxide (baseline: 22.8 [16.3] ppm; week 12: 5.3 [10.1] ppm) than those who terminated early (baseline: 23.7 [13.5] ppm; early termination visit: 19.2 [13.7] ppm).

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