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Does the Use of Varenicline for Smoking-Cessation Therapy Create or Increase Depression in Patients Without Existing Depressive Illness?

Brett R. Brown
Philadelphia College of Osteopathic Medicine, brettbr@pcom.edu

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the use of varenicline for smoking-cessation therapy creates or increases depression in patients without existing depressive illness.

STUDY DESIGN: Review of two randomized controlled trials published in 2011 and one observational cohort study published in 2009, all English language.

DATA SOURCES: Two randomized, double-blind, controlled clinical trials comparing varenicline to placebo in smoking cessation, and one observational cohort study comparing varenicline use within subjects. All articles were found using PubMed and EBSCO.

OUTCOMES MEASURED: Changes in depression was evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS), and adverse events were recorded and classified into depression-related according to the Medical Dictionary for Regulatory Activities version 12 and, in the observational cohort study, the British Drug Safety Research Unit standards.

RESULTS: Bollinger et al. and Garza et al. demonstrated a present but nonsignificant increase in depressive adverse events associated with varenicline use. Garza et al. reported a similarly small and nonsignificant worsening in MADRS score in the varenicline arm. Kasliwal et al. reported a nonsignificant change in depressive adverse events.

CONCLUSIONS: Results of the three studies show that there is inconclusive evidence regarding a link between varenicline and new-onset depression in smoking cessation. None of the studies demonstrated any significant relationship between varenicline and depression or depressive adverse events, but limitations in study design prevent the results from convincingly addressing such a relationship. The results encourage further studies designed both to assess varenicline's relationship with depression and to account for the varenicline's higher quit rate as a possible source of depressive changes.

KEY WORDS: varenicline, depression, randomized, adverse

INTRODUCTION

Smoking is a prominent risk factor for a wide variety of pathologies, and remains a common component of patient social histories. The addictive nature of smoking renders smoking cessation difficult for most patients, and drug-assisted methods are increasingly being considered in the quitting process.[5] One such drug, varenicline, can be effective but remains controversial due to concerns of depression-related adverse effects.[13]

An estimated 45.3 million U.S. adults smoke cigarettes—about 19.3% of the U.S. population greater than 18 years of age.[6] While smoking-related health care visits have proven too numerous to track reliably, smoking-attributable deaths in the U.S. average approximately 443,000 per year.[5] Because of cigarette smoking's combination of systemic effects and addictive pharmacodynamics, annual health-related economic losses in the U.S. are estimated at $193 billion—more than 10% of total U.S. annual healthcare expenditures.[5] Cost estimates are not limited to the macro-scale; one longitudinal analysis considered health-care costs, opportunity costs and other assorted factors, and estimated an effective per-pack cost to regular smokers of almost $40.[15] Smoking cessation with varenicline typically costs between $50 and $192 per month, with a typical regimen lasting 3 months.[7]

Smoking addiction has been principally traced to the agonistic effects of nicotine on nicotinic acetylcholine receptors, which preferentially release dopamine in the central nervous system. As with other addictive dopaminergic compounds (e.g., cocaine, opiates), this reinforces addictive behavior and, with dependence, causes withdrawal symptoms when absent. Recent studies have demonstrated evidence of addiction within only weeks of smoking and, in some individuals, within only days.[8] Withdrawal symptoms stem from nicotine-induced down-regulation of dopamine and other neurotransmitters, the deficiency of which can cause headache,

anxiety, nausea, dysphoria, depression, paresthesias, and intense cravings. Beyond its neurologic effects, cigarette smoking produces profound deleterious changes elsewhere in the body. Carcinogenic effects increase rates of lung cancer, along with cancers of the mouth, larynx, pharynx, sinuses, esophagus, liver, pancreas, stomach, kidney, bladder, cervix, bowel, and blood. Increases in blood viscosity exacerbate ischemic disease. Breathing allergies are aggravated, and smoking can create or worsen obstructive pulmonary disease.

Smoking cessation is a significant and difficult process; the majority of smokers indicate they would like to quit, about 36% make an annual attempt to quit, and only 3% successfully remain smoking-abstinent after six months.[13] Traditional strategies for smoking-cessation have generally been unassisted: self-imposed abrupt cessation ("cold turkey") or gradual cessation ("weaning"), or assisted: group therapy, psychosocial therapy, or long-term counseling. More recently developed assisted strategies utilize pharmacotherapy, with the hope of improving on the poor long-term quit rates of traditional efforts. Drug-assisted strategies fall into two categories: nicotine-replacement therapy (NRT), and psychoactive therapy. NRT has shown some efficacy coupled with a low adverse-event profile, but its long-term efficacy has proven questionable.[1] The two mainstays of psychoactive therapy are bupropion SR—an atypical antidepressant—and varenicline—a nicotine receptor partial agonist. Both medications have demonstrated improved efficacy over both traditional methods and NRT, but epidemiological surveillance and case reports have raised concerns regarding neuropsychiatric adverse events; the U.S. Food and Drug Administration (FDA) has issued a Black Box Warning of neuropsychiatric symptoms and suicidality for both drugs.[3,13] Varenicline has been shown to have the highest efficacy of smoking cessation options, but depression and suicide may be very serious side effects of the drug—especially in patients with no prior history of depressive illness, who may

suffer dangerous depressive symptoms before they are identified by the patient or healthcare provider.[3,4] This selective evidence-based medicine review evaluated two randomized, placebo-controlled, double-blind studies and one observational cohort study to examine the depressive adverse effects of varenicline in smoking cessation.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the use of varenicline for smoking-cessation therapy creates or increases depression in patients without existing depressive illness.

METHODS

The population chosen adult smokers ≥ 18 years of age, with the RCTs further selecting subjects that smoked an average of 10+ cigarettes a day during the previous year, with no period of abstinence greater than 3 months. The intervention studied in the RCTs was varenicline in its standardized dosing schedule: 0.5 mg QD for 3 days, followed with 0.5 mg BID for 4 days, followed by 1 mg BID for 11 weeks. The observational cohort study reported the majority but not entirety of subjects using the standardized dosing schedule. For the RCTs, comparisons were made between varenicline and visually-matched placebo of identical dosage and schedule. Measured outcomes that are being utilized were neuropsychiatric adverse events (AEs) of a depressive type—including suicide attempt—and changes in depressive mood index.

Key words used in the searches were "varenicline," "depression," "randomized," and "adverse." All articles were published in peer-reviewed journals and in the English language. The author searched the articles through PubMed and EBSCO, and selected articles based on relevance to the clinical question and inclusion of patient-oriented outcomes (suicide, depressive-type AEs, or worsened index of depression). Inclusion criteria consisted of studies where design

was either prospective or randomized, double-blind, placebo-controlled, studies that included patient-oriented outcomes, and studies of adult smokers > 18 years of age. Exclusion criteria consisted of studies with exclusively disease-oriented outcomes, studies that did not track adverse event data independent of efficacy data, and studies of smokers < 18 years of age. The statistics reported in the studies included mean change from baseline, 95% confidence interval (CI), and p-value.

OUTCOMES MEASURED

Outcomes measured were based on a psychiatric index of depression and incidence of reported AEs. The index utilized was the Montgomery-Åsberg Depression Rating Scale (MADRS).[12] The MADRS measures depressed mood using a 10-item list, with each item having a range of 0 (least severe) to 6 (most severe). Each item assesses a different aspect of depression: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. AE reporting was coded and categorized based on the Medical Dictionary for Regulatory Activities version 12 and, in the observational cohort study, the British Drug Safety Research Unit standards.

RESULTS

The two randomized, controlled trials in this review compared varenicline to placebo, and the observational cohort study compared varenicline within-subjects at 1-month intervals.

The study by Bollinger et al. was a randomized placebo-controlled study that included 593 participants randomized into two intervention arms, of which 492 completed the study (83%). 394 subjects were assigned to the varenicline arm, with 336 completing (85%), and 199 subjects were assigned to the placebo arm, with 156 completing (78%). Duration of follow-up was 16

Table 1 - Demographics & Characteristics of included studies

Study	Type	Pts. (n)	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bollinger et al. (2011) [2]	Double-blind RCT	593	18–75 y/o	Adult smokers (18–75 y/o) with BMI 15–38, weight of 45.5+ kg, that smoked an average of 10+ cigarettes/day during the previous year and with no period of abstinence > 3 months.	Women of childbearing age that refused birth control methods during the study; any current or past history of psychiatric illness including present or past suicidal behavior, ideation or attempts; severe unstable medical condition; past history of varenicline use; concurrent use of smoking cessation medications; concurrent enrollment in other clinical trials	101	Varenicline; dosage schedule: 0.5 mg q.d. x 3 days, then 0.5 mg b.i.d. x 4 days, then 1 mg b.i.d. x 11 weeks
Garza et al. (2011) [9]	Double-blind RCT	110	18–75 y/o	Adult smokers (18–75 y/o) that smoked an average of 10+ cigarettes/day during the previous year and with no period of abstinence > 3 months	Women of childbearing age that refused birth control methods during the study; any current or past history of psychiatric illness including present or past suicidal behavior, ideation or attempts; severe unstable medical condition; past history of varenicline use; concurrent use of smoking cessation medications; concurrent enrollment in other clinical trials	22	Varenicline; dosage schedule: 0.5 mg q.d. x 3 days, then 0.5 mg b.i.d. x 4 days, then 1 mg b.i.d. x 11 weeks
Kasliwal et al. (2009) [10]	Prospective cohort study	2682	> 18 y/o	Adult smokers part of the English National Health Service (NHS)	None	117	Varenicline; dosage schedules not consistently specified; 73.6% of subjects clearly reported the standard 1 mg b.i.d. dosing

weeks, with adverse events (AEs) recorded up to 30 days after the administration of the last dose of the intervention. For purposes of this review, AEs were treated as the sum of AE categories "Depressed mood disorders or disturbances" and "Suicidal and self-injurious behaviors." No statistical significance in AE incidence was found between the varenicline and placebo groups ($p > .05$). Table 2 shows incidence of depressive AEs, where there was a small but nonsignificant difference of AE incidence in the varenicline group (36%) compared to the placebo group (35%). The relative risk increase (RRI) was calculated to be 57.1% and absolute risk increase (ARR) was 0.1%. Numbers needed to harm (NNH) was calculated as 1,000, meaning 1,000 patients need to be treated with varenicline for 1 patient to suffer an additional depressive AE.

Table 2: Incidence of depressive adverse events

CER	EER	RRI	ARI	NNH	P
35%	36%	2.9%	0.1%	1,000	> .05

The study by Garza et al. was a randomized placebo-controlled study that included 110 participants randomized into two intervention arms, of which 88 completed the study (80%). 55 subjects were assigned to the varenicline arm, with 39 completing (71%), and 55 subjects were assigned to the placebo arm, with 49 completing (89%). Duration of follow-up was 16 weeks, with additional follow-up conducted for subjects categorized as "lost to follow-up" in the original study duration. While a "worst-case" analysis was not done on all subjects lost to follow-up, the additional post-study follow-up determined that AEs accounted for only 3 of the 16 subjects lost in the varenicline group. Changes in depressive mood were measured by deviation from baseline MADRS scores for the varenicline group (LS mean ± SE: 1.52 ± .21) and placebo group (LS mean ± SE: 1.50 ≠ .28), as shown in table 3. No significant difference was found between the two arms (difference = .03, 95% CI —.68–.73; $p > .05$). For purposes of this review, adverse events were treated as the AE category "Depressed mood disorders or

disturbances;" no suicidal events were reported. No significance in AE incidence was found between the varenicline and placebo groups ($p > .05$). Table 4 shows incidence of depressive AEs, where there was a small but nonsignificant difference of AE incidence in the varenicline group (11%) compared to the placebo group (9.1%). The relative risk increase (RRI) was calculated to be 21% and absolute risk increase (ARI) was 1.9%. Numbers needed to harm was calculated as 52, meaning 52 patients need to be treated with varenicline for 1 patient to suffer an additional depressive AE.

Table 3: Change from baseline MADRS total score (LS mean ± SE)

Placebo	Varenicline	Difference	P
1.50 ± .28	1.52 ± .21	0.03 (95% CI —.68–.73)	> .05

Table 4: Incidence of depressive adverse events

CER	EER	RRI	ARI	NNH	P
9.1%	11%	21%	1.9%	52	> .05

The study by Kasliwal et al. was the initial report of an ongoing observational cohort study of 2,682 patients in the British National Health Service (NHS). While the study utilizes ongoing monthly questionnaires, the data reported represent the 4 months following the first prescription of varenicline for each given patient. For the purposes of this review, 44 patients with a significant psychiatric past medical history (PMH) are excluded, and so the population of consideration is 2,638. The 4-month incidence of depressive adverse events was 15 (0.57%), and of suicidal ideation was 1 (0.04%). After accounting for the aforementioned exclusion, no suicidal events were reported. Though the study was not designed or powered for between-groups comparison, a recent study of overall depression rates within the NHS found a mean 4-month incidence of combined depressive symptoms and depression diagnoses of 0.83%.[14] While no protective effect of varenicline is presumed, the incidence of depression in the study's

population was lower than the mean incidence of a larger NHS sample, as seen in table 5.

Table 5: Incidence of depressive symptoms

	Kasliwal et al. [10] (n=2,638)	Rait et al. [14] (n=2,982,024)	Difference
Mean 4-month Incidence	0.57%	0.83%	—0.26%

DISCUSSION

This literature review investigated the possibility that the use of varenicline for smoking cessation therapy might create or worsen depression in patients without known depressive illness. The studies by Bollinger et al. and Garza et al. were randomized, controlled trials that failed to find a significant difference in new-onset depression between subjects taking varenicline and those taking placebo. The study by Kasliwal et al. established reports of new-onset depressive symptoms, but at a rate that was lower than an NHS mean for a similar time span.

Limitations were present in each study that affect their validity regarding the question of concern. Kasliwal et al. utilized a large cohort size but by the observational nature of the study design, no significant causal links can be drawn between varenicline and depression. Indeed, the results of that study might seem to indicate a protective effect of varenicline, but such a conclusion would be subject to significant sampling bias given the breadth of the NHS sample for depression incidence (e.g., the broader NHS data account for all patients in the sample population, not only those engaged in smoking-cessation therapy). That study is further limited by the collection of data as reliant upon General Practitioner submission, adding both another possible sampling bias to the consideration and inconsistent/missing values from some questionnaires that "diluted" the overall data set.

Both Bollinger et al. and Garza et al. acknowledged financial support by Pfizer, Inc., the U.S. marketer of the Chantix® brand of varenicline. Bollinger et al. also acknowledged that their study was principally powered for efficacy analysis, limiting the extent of significance that could be established for adverse events reported. Similarly, while the study by Garza et al. was specifically designed to assess neuropsychiatric AEs, its lack of a predefined hypothesis prevented the application of more rigorous statistical comparisons (e.g., *t*-test, ANOVA, ANCOVA). Garza et al. also note that their study population was restricted to smokers willing and able to commit to a 2-week inpatient period, which raises the concern of sampling bias and reduced external validity.

Perhaps most importantly, no studies yet published—including those in this review—have adequately addressed two key points: 1) Smoking cessation itself is understood to be a possible aggravating factor in depression or suicide.[11] If there is an increased link between varenicline and depression, is it a direct consequence of the drug's pharmacology or a statistical consequence of the drug's efficacy? In other words, do more varenicline patients become depressed because more of them successfully quit smoking? 2) While new-onset depression is an undesirable POEM by itself, suicide is both a worse outcome and a rarer one. Even in Kasliwal et al., a large sample size (n=2,682) yielded only 6 suicide-related events, of which 5 were in patients with PMH significant for psychiatric illness. Tracking such an outcome properly requires either a significant sample size or a series of RCTs—powered to assess suicide rate differences—that could be collapsed across a meta-analysis.

CONCLUSION

The studies reviewed collectively are inconclusive regarding varenicline's influence on new-onset depression. While the lack of significance found in the comparisons by Garza et al.

and Bollinger et al. point toward a lack of causal link between varenicline and depression, limitations both in the design and implementation of those studies prevent that conclusion from being firmly supported. Likewise, the study by Kasliwal et al. suffers limitations in design that, without strong evidence from either other study, hinder its use in conclusively proving or disproving a causal link between varenicline and new-onset depression.

More-substantial clinical research has established a link between varenicline and adverse neuropsychiatric outcomes other than depression, and varenicline continues to carry an FDA Black Box warning.[13] Further, there is stronger evidence of a deleterious effect of varenicline when used by patients with existing depressive illness. While this literature review indicates no significant association between varenicline and depressive events, it does not reliably rule out that such an association exists. Cantrell et al. and others recommend that varenicline remain a second-line treatment option, and further suggest that some form of depression screening should be administered to all patients prior to varenicline use.

Ideally, future research into varenicline's safety will focus on two points. First, if there is a difference in depressive events with varenicline use, is it due directly to the drug's neuropsychiatric effects or its improved quit rate? Second, does careful screening and proactive mental health management improve outcomes for patients taking varenicline? Until both questions are addressed with greater confidence, varenicline may have an uncertain role in modern smoking cessation therapy.

References

1. Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco Control*. 2013;22:32-37. doi: 10.1136/tobaccocontrol-2011-050129

2. Bolliger CT, Issa JS, Posadas-Valay R, et al. Effects of varenicline in adult smokers: A multinational, 24-week, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2011;33(4):465-477. doi: 10.1016/j.clinthera.2011.04.013.

3. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews*. 2011;2. doi: 10.1002/14651858.CD006103.pub5.

4. Cantrell M, Argo T, Haak L, Janney L. Adverse Neuropsychiatric Events Associated with Varenicline Use in Veterans: A Case Series. *Issues in Mental Health Nursing*. 2012;33:665-669.

5. Centers for Disease Control and Prevention. Smoking-Attributable Mortality, Years of Potential Life Lost, and Productivity Losses—United States, 2000–2004. *Morbidity and Mortality Report 2008*;57(45):1226-8.

6. Centers for Disease Control and Prevention. Vital Signs: Current Cigarette Smoking Among Adults > 18 Years—United States, 2005–2010. *Morbidity and Mortality Report 2011*;60(33):1207-12.

7. Chantix: Cost and Formulation. *Pfizer for Professionals* (website). http://www.pfizerpro.com/hcp/chantix/cost-formulation. Accessed Sep 14, 2012.

8. DiFranza JR & Wellman RJ. A sensitization-homeostasis model of nicotine craving, withdrawal, and tolerance: Integrating the clinical and basic science literature. *Nicotine & Tobacco Research*. 2005;7(1):9-26.

9. Garza D, Murphy M, Tseng LJ, Riordan HJ, Chatterjee A. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. *Biol Psychiatry*. 2011;69(11):1075-1082. doi: 10.1016/j.biopsych.2010.12.005.

10. Kasliwal R, Wilton LV, Shakir SAW. Safety and drug utilization profile of varenicline as used in general practice in England. *Drug Safety*. 2009;32(6):499-507.

11. Mendelsohn C. Smoking and depression: A review. *Australian Family Physician*. 2012;41(5)

12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*. 1979;134:382-389.

13. Moore TJ, Furberg CD, Glenmullen J, et al. Suicidal behavior and depression in smoking cessation treatments. *PLoS ONE*. 2011;6(11):e27016. doig: 10.1371/journal.pone.0027016.

14. Rait G, Walters K, Griffin M, et al. Recent trends in the incidence of recorded depression in primary care. *The British Journal of Psychiatry*. 2009;195:520-524. doi: 10.1192/bjp.bp.108.058636.

15. Sloan FA, Ostermann J, Conover C, et al. *The Price of Smoking*. Cambridge, MA: The MIT Press; 2004.