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Smoking Cessation After Brain Damage Does Not Lead to Increased Depression: Implications for Understanding the Psychiatric Complications of Varenicline

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Abstract

Background—There are concerns that varenicline (Chantix/Champix), a prescription medication used to treat smoking addiction, might cause serious neuropsychiatric side effects, such as depression, self-injurious behavior, and suicide. However, the cause of depression and related symptoms in persons who quit smoking after taking varenicline remains uncertain, because smoking cessation itself can cause such symptoms.

Method—We studied 70 patients with brain lesions: 32 had stopped smoking after suffering their lesion (Quitters) and 38 had kept smoking (Non-Quitters).

Results—There was no indication of increased depression in the Quitters compared to the Non-Quitters. The 2 groups, which were statistically indistinguishable on demographic and neuropsychological variables, showed the same rates and levels of severity of depression and related symptoms. Moreover, in a subgroup of 16 Quitters who had stopped smoking immediately after their neurological injury in the context of losing their craving to smoke, rates of depression-related symptoms were no higher than in the other Quitters and the Non-Quitters.

Conclusions—Smoking cessation did not lead to elevated levels of depression in patients with brain lesions, suggesting that psychiatric complications (particularly depression) observed after varenicline use are caused by the medication rather than the smoking cessation itself.

Keywords

smoking cessation; depression; brain damage; nicotine withdrawal; varenicline

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Introduction

Varenicline (trade name Chantix in the U.S., and Champix in Canada, Europe, and elsewhere) is a prescription medication that has been widely used to treat smoking addiction. Its main mechanism of action is as a partial agonist at the $\alpha_4\beta_2$ subtype of the nicotine acetylcholine receptor.¹ This receptor, in the ventral tegmentum, is believed to mediate the dependence-producing properties of nicotine.² As a partial agonist at this receptor, varenicline presumably reduces cravings for nicotine and reduces the pleasurable effects of cigarettes and other tobacco products. This action can help people stop smoking and prevent relapse.

Varenicline has been FDA-approved in the U.S. since 2006. It is 1 of 7 medications approved for tobacco dependence treatment in most countries; the other drugs are the nicotine patch, gum, lozenge, inhaler or nasal spray, and bupropion. Several large-scale clinical trials indicate that varenicline is quite effective. It has outperformed the other medications, nonpharmacologic approaches, and placebo, with superior short- and long-term abstinence rates and better relapse prevention rates³⁻¹² That varenicline has been shown effective for smoking cessation in psychiatric populations¹³⁻¹⁶ is particularly important, given the high base rates of smoking addiction in people with mental health disorders.¹⁷

The literature indicates that, in many respects, varenicline has an acceptable safety and tolerability profile. The most common side effects are nausea, abnormal dreams, sleep disorders, and headaches. In most patients, these side effects are mild to moderately severe, and in many patients they subside over time.^{9, 10, 18, 19} However, some patients using varenicline reportedly experience serious psychiatric symptoms, such as depression, suicidal ideation, and even self-injurious and suicidal behavior.^{20, 21} Determining whether varenicline plays a causal role in the development of depression and other psychiatric symptoms, though, can be challenging, especially because smoking cessation itself can lead to similar effects, such as depression, anxiety, and elevated stress.²²⁻²⁴

It could be that varenicline causes the psychiatric problems directly via a pharmacological mechanism, or the cause could be smoking cessation and nicotine withdrawal. This ambiguity has not been fully resolved in studies to date. As Jiménez-Ruiz et al¹⁰ note, it remains unclear whether the association of varenicline with adverse neuropsychiatric effects is causal, coincidental, or related to smoking cessation. Cahill et al⁹ agreed, pointing out that many of the behavioral and mood changes reported to be associated with varenicline may actually be associated with nicotine withdrawal, although the authors acknowledged that some adverse effects have occurred in persons who continued to smoke while taking varenicline.

We had an unusual and compelling opportunity to address this issue using a neurological approach. Within a group of neurological patients who smoked and were nicotine-addicted before their brain injury, we identified a subset who, after the acute onset of focal brain damage, had abruptly stopped smoking.²⁵ In our initial publication, we emphasized the neuroanatomical correlates of this finding. We identified the insula as a key brain structure that, when damaged, could lead to loss of urges and cravings to smoke in some patients, thereby contributing to smoking cessation (also see Naqvi and Bechara²⁶).

In the current study, we returned to the dataset to explore the occurrence of depression and related symptoms in our neurological patients, capitalizing on the fact that the patients have been extensively studied with psychological and neuropsychological tests that allow comprehensive characterization of their behavioral and emotional status. We contrasted a cohort of patients who had stopped smoking after their brain lesions (Quitters) with a cohort

who had kept smoking (Non-Quitters), focusing on the development of depression and related symptoms as the key outcome variables.

Within the Quitters group, we also investigated depression outcomes in the subset of patients who had stopped smoking immediately after they sustained their brain injury because they had suddenly lost their urges and cravings to smoke. This scenario closely models what has been hypothesized to occur in varenicline-treated quitters, thus giving us a rare research opportunity. Smokers who quit with the aid of varenicline may experience depression and mood instability that persist well beyond when symptoms of nicotine withdrawal should have abated.²⁷ Moreover, it has been reported that varenicline users with no prior psychiatric history have developed depression and suicidal ideation that persisted over months or years.³

The basic objective of this study was to determine whether our neurological patients who had quit smoking without the use of medication had higher acute and long-term rates of depression and related symptoms than our neurological patients who had kept smoking. A finding that depression rates were not higher would support the idea that depression-related psychiatric manifestations in varenicline-treated smokers result from the drug's direct pharmacological actions, rather than from the smoking cessation per se, or, put another way, that the adverse neuropsychiatric manifestations associated with varenicline use must be pharmacologically induced.

METHODS

Participants

Our participants were 70 neurological patients who had been studied by Naqvi et al in 2007.²⁵ Of our 70 patients, 57 had had a stroke and 13 had sustained a brain injury through surgery to resect a benign tumor or to treat pharmacoresistant epilepsy. The 70 patients had been selected for the original study because they were nicotine-dependent smokers who had been smoking more than 5 cigarettes per day for longer than 2 years when they suffered their brain injury.

The patients were drawn from the Iowa Patient Registry maintained in the Department of Neurology at the University of Iowa College of Medicine, under the auspices of which their brain lesions²⁸ and neuropsychological and psychological status²⁹ had been extensively characterized. To be eligible to enroll in the Registry (which is a general resource maintained for scientific purposes ranging well beyond those of Naqvi et al²⁵ and the current study), the patients had to be free of any premorbid history of primary psychiatric disease, alcohol or substance abuse (other than nicotine), learning disability, and dementia. For the current study, the patients also had to be capable of valid performances on the mood and personality measures that we used. We excluded patients with severe chronic aphasia or severe chronic reading comprehension deficits, as determined by neuropsychological assessment. None of the patients were treated with varenicline or other anti-smoking medications after the onset of their brain lesions or during data collection for the current study.

We used the Naqvi et al²⁵ classification to divide the patients into 2 groups: (1) Quitters: 32 patients who had stopped smoking after their brain lesions; and (2) Non-Quitters: 38 patients who had kept smoking after their brain lesions. To measure each patient's smoking behavior both before and after lesion onset, we conducted a structured interview with the patient and, when needed, a collateral informant such as a spouse or child. We recorded the number of cigarettes smoked per day at lesion onset, current number of cigarettes smoked per day by current smokers, and number of years of smoking at lesion onset (see Supplemental

Materials in Naqvi et al²⁵). Table 1 lists demographic characteristics and neuropsychological test results for the 2 groups.

Measurement of Depression and Related Symptoms

We assessed the patients for depression and related symptoms in the acute epoch immediately following their brain lesions (defined as within the first 2 weeks following the onset of brain injury), and again in the chronic epoch (defined as 3 or more months after lesion onset, when neurological and cognitive recoveries had stabilized). For the acute epoch, we used clinical and behavioral observational data (see below) obtained from the patients' clinical and research files, and formulated a Depression Rating. For the chronic epoch, we again formulated a Depression Rating based on clinical observations, and we also used formal measurement instruments designed to detect and quantify depressive symptoms: the Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), and Minnesota Multiphasic Personality Inventory-2 (MMPI-2) Clinical Scales 2 (D), 7 (Pt), and 8 (Sc).

Depression Ratings—The patients in this study had been evaluated acutely during their hospitalization, immediately following the onset of their neurological event, by board-certified clinical neurologists and neuropsychologists in our research team. The patients were also evaluated by clinical neuropsychologists at their neurology-related outpatient visits to our facility during the chronic recovery epoch, and the clinical observations were documented by notes in the patients' files. Thus, there were extensive observations in the medical records and research files about the patients' psychological status, behavior, and overall clinical presentation. (Depression is a common manifestation in neurological patients, and our clinical staff neuropsychologists and neurologists are especially vigilant for possible depressive symptoms in the patients whom we recruit into our Patient Registry.) For purposes of the current study, these records were reviewed to ascertain any observations or descriptions indicative of depression or related symptoms. Affective, behavioral, cognitive, and somatic symptoms of depression and anxiety were recorded. The review of medical records was conducted by a member of the research team (A.M.) who was blind to the group status of the patients and to the research question of the current study at the time of her review and recording.

For both the acute and chronic epochs, the medical record data were used to formulate a variable of Depression Rating. Patients were classified as having depression on a scale of 0 (none), 1 (mild), or 2 (moderate/severe), for both the acute (Depression Rating Acute) and chronic (Depression Rating Chronic) epochs. In addition, for the chronic epoch, we used the medical record data to determine whether patients had clinically significant depression (Clinical Depression, in a binary yes or no manner) according to DSM-IV Criterion C under Major Depressive Episode—whether patients had depression symptoms that caused “clinically significant distress or impairment in social, occupational, or other important areas of functioning”³⁰ (American Psychiatric Association, 1994, p. 327). This determination was performed by a board-certified neuropsychologist who was blind to the research question of this study and the group status of the patients. (We did not perform this assessment for the acute epoch. Given that many patients were hospitalized for a portion of this epoch, and were in the acute phase of recovery from neurological illness (eg, undergoing inpatient rehabilitation), the determination of “impairment in social, occupational, or other important areas of functioning” would have been confounded with the patients' basic medical situation, and impossible to assess reliably and meaningfully.) In sum, the medical record data provided the basis for deriving Depression Rating Acute, Depression Rating Chronic, and Clinical Depression variables.

Beck Depression Inventory-II (BDI-II)—The BDI-II was administered in the chronic epoch. The BDI-II detects and measures the severity of depression, with 21 items tapping various symptoms and attitudes.³¹ Each item deals with a particular aspect of depression (eg, mood, sense of self-worth, suicidal ideation, appetite, libido), and whether and to what extent that problem has been present over the past 2 weeks. Each item contains 4 statements of graded severity expressing how the person might feel or think about the aspect of depression under consideration. The statements carry scores ranging from 0 for absence of problems in that area to 3 for the most severe level of the problem.

Total scores were calculated and graded for overall depression severity according to the BDI-II Manual: scores of 0-13 were classified as “minimal depression”; scores of 14-19, “mild depression”; scores of 20-28, “moderate depression”; and scores of 29-63, “severe depression.” Also, given that suicidal ideation and behavior have been implicated in the psychiatric side-effect penumbra of varenicline, we looked specifically at Item 9 on the BDI-II, which deals with “Suicidal Thoughts or Wishes” and is graded from 0 (“I don’t have any thoughts of killing myself”) to 3 (“I would kill myself if I had the chance”). The average time between lesion onset and BDI-II administration did not differ significantly between the Quitters and Non-Quitters, as determined by a *t* test ($P > 0.05$). In both groups, the majority of patients received the BDI-II between 3 and 24 months post lesion onset.

Beck Anxiety Inventory (BAI)—The BAI was administered in the chronic epoch. The BAI detects and measures the severity of anxiety.³² It contains 21 typical symptoms of anxiety, which are rated on a 4-point scale ranging from “not at all” to “severely—I could barely stand it.” Patients rate how much they have been bothered by the symptom during the past week, including today. Ranges of severity suggested by the BAI Manual are as follows: scores of 0 – 7 are “minimal anxiety”; scores of 8 – 15, “mild anxiety”; scores of 16 – 25, “moderate anxiety”; and scores of 26 – 63, “severe anxiety.” The average time between lesion onset and BAI administration did not differ significantly between the Quitters and Non-Quitters, as determined by a *t* test ($P > 0.50$). In both groups, the majority of patients received the BAI between 3 and 14 months post lesion onset.

Minnesota Multiphasic Personality Inventory-2 (MMPI-2)—The MMPI-2 was administered in the chronic epoch. We selected 3 clinical scales from the MMPI-2³³ that are commonly used to measure depression, anxiety, and general psychological distress: Clinical Scales 2, 7, and 8. (In the traditional MMPI nomenclature, these scales carry verbal labels: 2 is labeled “D,” for “depression”; 7 is labeled “Pt,” for “psychasthenia” or “anxiety”; and 8 is labeled “Sc,” for “schizophrenia”. While still used by some clinicians as a form of shorthand for ease of communication, the labels do not map onto clinical diagnoses, and we will not use them further in this article.) Elevations on any of these scales, as well as the 2-7 and 2-7-8 MMPI-2 “profiles” (whereby the 2 and 7—or 2, 7, and 8—scales are clinically elevated above a T-score of 65, and above other clinical scales) are associated with psychological distress and depression, and are among the most common profiles in persons who present for psychotherapeutic services and among outpatient and inpatient psychiatric populations (eg, Greene, 1991³⁴). The average time between lesion onset and MMPI-2 administration did not differ significantly between the Quitters and Non-Quitters, as determined by a *t* test ($P > 0.40$). In both groups, the majority of patients received the MMPI-2 between 3 and 36 months post lesion onset.

Data Quantification and Analysis

To contrast the Quitters and Non-Quitters on the various depression variables, we used parametric tests (*t* tests) and, where appropriate, nonparametric tests for proportional data (Chi Square Test, Fisher’s Exact Test). The tests were corrected for multiple related

comparisons, and the contrasts were 2-tailed. For the Depression Ratings (Acute and Chronic), we used *t* tests and analyzed the ratings qualitatively. For the dichotomous Clinical Depression variable, we contrasted the groups using Fisher's Exact Test. For the BDI-II and BAI, we analyzed the raw scores; for MMPI-2 Clinical Scales 2, 7, and 8, we analyzed the T-scores; and for all of these measures, we compared the Quitters and Non-Quitters using *t* tests. We analyzed BDI-II Item 9 both quantitatively with a *t* test, and qualitatively. We analyzed the demographic and neuropsychological data with either parametric (*t* tests, corrected for multiple comparisons where necessary) or nonparametric tests, as appropriate.

RESULTS

Demographic and Neuropsychological Variables

The Quitters and Non-Quitters showed no statistically significant differences in age, sex ratio, education, handedness, medications, intellectual functioning, or neuropsychological measures (Table 1). In both groups, most patients' brain damage had been caused by stroke, and a few by surgery; the Quitters had a higher proportion of strokes, but this difference was not relevant to the focus of our study. We did not test medications acute statistically because of the low number of observations in each group.

Outcomes for Depression and Related Symptoms

Table 2 lists the main outcomes of the analyses of depression and related symptoms. There were no significant differences between the Quitters and Non-Quitters on any of the outcome measures.

Acute Epoch—There were no significant differences between the Quitters and Non-Quitters in depression outcomes. The groups had statistically indistinguishable mean scores on the Depression Rating Acute (0.25 and 0.39, respectively). Looking at these ratings qualitatively, we found no Quitters who had ratings greater than 0, and 3 patients in the Non-Quitters group (8%) who had ratings greater than 0. Thus, the percentage of patients in each group who had some degree of depression and related symptoms was similar.

Chronic Epoch—We found no notable differences between the Quitters and Non-Quitters in terms of depression and related symptoms. The Quitters and Non-Quitters had statistically indistinguishable scores on the Depression Rating Chronic measure (0.47 and 0.68, respectively). In qualitative terms, we found 5 Quitters (16%) who had Depression Rating Chronic ratings greater than 0, and a similar number of 9 Non-Quitters (24%). For the Clinical Depression variable, the 2 groups were not significantly different: 10 Quitters and 16 Non-Quitters had clinically significant depression. Numerically, the rate of depression was actually somewhat higher among Non-Quitters than Quitters (42% versus 31%).

For the BDI-II, the mean scores did not differ statistically: 10.1 for Quitters and 12.3 for Non-Quitters. According to the Manual for the BDI-II,³¹ these scores fall within the "minimal depression" range. Likewise, mean scores for BDI-II Item 9 (suicidal ideation) did not differ statistically: 0.13 for Quitters and 0.18 for Non-Quitters. Moreover, the 2 groups had similar severity of suicidal ideation: no Quitter and only 1 Non-Quitter reported a severity level above 1 (level 1 corresponds to "I have thoughts of killing myself, but I would not carry them out"). None of the patients in either group had a post-lesion history of a suicide attempt or completed suicide.

For the BAI, the mean was somewhat higher in Non-Quitters (13.0) than Quitters (8.5), but the difference was not statistically significant. According to the Manual for the BAI,³² both groups' scores were within the "mild anxiety" range.

For MMPI-2 Scales 2, 7, and 8, the Quitters and Non-Quitters had similar average T-scores. Moreover, all the scores were below the threshold of "clinically significant" elevation (T-score = 65; 1.5 standard deviations above the mean).

We looked further for potential differences between the groups in depression outcomes. We checked each group for patients who had substantially elevated scores on the BDI-II, MMPI-2 Scale 2, or both. For this analysis, the BDI-II score had to be 20 or higher ("moderate" depression or worse), and the MMPI-2 Scale 2 T-score had to exceed 65. Again, we found no significant between-group differences: 10 Quitters (31%) and 16 Non-Quitters (42%) met this classification.

The proportion of patients taking antidepressant or anti-anxiety medication in each group was not significantly different ($P = 0.70$), but because such medications could affect the depression and anxiety measures, we re-ran all of the statistical contrasts for the chronic epoch variables shown in Table 2 after excluding these medication-treated patients. We contrasted 29 Quitters (having removed the 3 patients on antidepressant medication) with 35 Non-Quitters (having removed the 3 patients on anti-anxiety medication, 1 of whom was also taking an antidepressant). None of the findings changed. All of the contrasts between the Quitters and Non-Quitters remained solidly non-significant. The P values for between-group contrasts of the 8 dependent measures for the chronic epoch in Table 2 ranged from 0.25 to 0.87. For the Clinical Depression rating, 9 Quitters (31%) and 15 Non-Quitters (43%) met the criterion of having clinically significant depression. In sum, when patients taking antidepressant and/or anti-anxiety medications were removed from the analyses, all of the findings remained the same.

Subdivisions of Quitters: Ease versus Difficulty

In the original Naqvi et al²⁵ study, the researchers subdivided the Quitters group into those who had stopped smoking with "ease," having no "further urge" to smoke (Quitters Ease, $n = 16$), and those who had stopped smoking with "difficulty," still fighting "urges" to smoke (Quitters Difficulty, $n = 16$). Because the Quitters Ease group provides an especially interesting model of varenicline-treated smoking quitters, we looked specifically at the development of depression and related symptoms in this group. Table 3 lists the relevant depression outcome variables calculated for the Quitters Ease and Quitters Difficulty subgroups. (These data had already been subjected to statistical analyses. We did not conduct any additional statistical tests for this follow-up investigation.)

The Quitters Ease and Quitters Difficulty subgroups were statistically indistinguishable on all of the measures—the 3 scales of Depression Rating Acute, Depression Rating Chronic, and Clinical Depression, and the 3 formal measures of BDI-II, BAI, and MMPI-2. For Clinical Depression (depression of sufficient severity to disrupt social, occupational, and other important areas of functioning), 3 of the Quitters Ease patients (19%) met this criterion, compared with 7 of the Quitters Difficulty patients (44%). On this measure, then, depression affected more than twice as many patients in the Quitters Difficulty subgroup. As shown in Table 2, the Non-Quitters also scored higher than the Quitters on this measure (42% versus 31%, respectively). The same trend of higher depression ratings for the Quitters Difficulty subgroup is evident in the Depression Rating (Acute and Chronic) measures. These findings run counter to the idea that, because of their similarities to varenicline-treated quitters, our Quitters Ease group would have more depression.

Overall, the Quitters Ease subgroup showed little indication of major or frequent depression or related symptoms. The mean BDI-II score (11.1) was in the range of “minimal depression,” and the mean BAI score (7.8) was at the bottom of the range for “mild anxiety.” None of the patients reported suicidal ideation on BDI-II Item 9. None of the mean T-scores on the 3 MMPI-2 scales reached clinically significant elevation. The Depression Ratings for the acute and chronic epochs both averaged less than 1.0 (0.13 and 0.31, respectively). In the acute epoch, no Quitters Ease patients had the highest rating of 2; in the chronic epoch, 2 patients had a rating of 2. In short, depression was infrequent in the Quitters Ease subgroup.

DISCUSSION

We found no indication of more frequent or more severe depression or related symptoms in neurological patients who had stopped smoking after sustaining a brain lesion than in patients who had kept smoking after sustaining brain damage. This finding held true in the acute epoch (the first 2 weeks after onset of the brain lesion) and the chronic epoch (3 months or longer after lesion onset). The finding held true in ratings derived from clinician observations, characterization of depression symptoms that were interfering with interpersonal and occupational functioning, reports of suicidal ideation and behavior, and formal measurements with the Beck Depression Inventory-II, Beck Anxiety Inventory, and Minnesota Multiphasic Personality Inventory-2.

Moreover, patients who had stopped smoking easily and abruptly, because of a sudden loss of “urges” and “cravings” to smoke (as found in Naqvi et al.²⁵), had no higher levels of depression or related symptoms than patients who had quit with difficulty and then struggled to fight off their urges and cravings to resume smoking. The “Quitters Ease” patients provide a useful model of varenicline-treated smoking quitters.

Our results cannot be attributed to demographic or neuropsychological variables. The patients who stopped or kept smoking were indistinguishable on such variables as age, sex, education, medication status, intelligence quotient (IQ), and several neuropsychological functions.

Overall, our findings in neurological patients did not support the idea that smoking cessation per se leads to increased depression and related symptoms. These findings would seem to throw the onus for psychiatric side effects of smoking cessation onto varenicline.

Early smoking cessation studies with varenicline seemed to show an acceptable safety and tolerability profile.^{9, 10, 18, 19} Beginning around 2007, reports began to appear indicating that some varenicline users had manifested serious psychiatric symptoms such as depression, agitation, behavioral changes, suicidal ideation, and even suicidal behavior. In early 2008, the FDA issued an Alert saying that “it appears increasingly likely that there is an association between Chantix and serious neuropsychiatric symptoms.” The FDA published an Early Communication³⁵ recommending that health care providers monitor patients taking Chantix for behavior and mood changes. In 2008, Pfizer, the main marketer of varenicline, updated the safety information for the drug and noted that some patients taking varenicline “have reported changes in behavior, agitation, depressed mood, suicidal thoughts or actions.” An analysis by the Institute for Safe Medication Practices reported similar kinds of serious psychiatric side effects of varenicline, including suicidal ideation and acts, psychosis, and hostility and aggression. In 2009, the FDA required varenicline to carry its strongest safety warning, a black box warning, about the risk of depression, suicidal thoughts, and suicidal actions.

Sorting out the potential role of varenicline in causing psychiatric manifestations has been challenging. The nicotine withdrawal syndrome associated with smoking cessation can include symptoms that overlap with those of major depression and anxiety disorders: low mood, irritability, poor concentration, sleep difficulties, and weight changes.^{36, 37} However, withdrawal symptoms last for only a few days or weeks, whereas varenicline side effects can last for months or longer.

Some studies have reported depression appearing after smoking cessation. In an extensive literature review, Aubin³⁸ concluded that there is evidence that smoking cessation can result in the new onset of major depressive disorder, even in persons with no history of depression. Hughes³⁹ also noted that stopping smoking seems to lead to major depression in some smokers, and could theoretically induce suicide. Still, in the few studies available, smoking cessation has never been directly and unequivocally linked to suicide. The appearance of psychiatric symptoms in quitters is one of the most potent reasons for treatment failure and relapse,⁴⁰⁻⁴² even among patients with smoking-related medical comorbidities such as cardiovascular⁴³ and cerebrovascular⁴⁴ disease, who would presumably be highly motivated to quit.

Several anecdotal and case reports, some of which have been dramatically chronicled in the popular media, have linked varenicline to aggression, homicide, and suicide.^{20, 21, 45, 46} In 2008, the US Federal Aviation Administration went so far as to ban the use of varenicline by pilots and air traffic controllers, citing concerns about possible adverse neuropsychiatric effects that could threaten public safety. The Institute for Safe Medication Practices has issued several reports showing that varenicline tops the list of drugs with adverse effects such as provoking self-injury and suicide. For example, the Institute's Quarter Watch report⁴⁷ noted that since being approved in 2006, varenicline has accounted for 3325 reported serious injuries in the United States alone, with 112 deaths.

Some controlled empirical studies, however, have argued against the idea that varenicline can cause depression or suicidal or violent behavior.^{9, 11, 19, 48, 49} One large-scale study⁵⁰ analyzed medical records from more than 80,000 people who were trying to stop smoking—more than 10,000 of whom were using varenicline—and could not link varenicline to an increased risk of depression, suicidal thoughts, or fatal or non-fatal self-harm. Still, a 2-fold increased risk of self-harm with varenicline could not be ruled out on statistical grounds. Kasliwal et al⁴⁸ noted that varenicline-treated patients with suicidal events had a history of psychiatric illness, a clear precipitating factor for the event, or both. Although several case reports have described adverse neuropsychiatric events related to varenicline treatment in patients with premorbid psychiatric conditions,⁵¹⁻⁵⁴ large-scale empirical studies in psychiatric populations have failed to show strong evidence of increases in such adverse events, even in these populations.^{13, 15, 16} Some positive effects of varenicline have even been reported, for example, improved cognitive performance and associated working memory-related brain activity, as measured with functional magnetic resonance imaging,⁵⁵ and a reduction in affective symptoms.⁵⁶

Some studies, though, have continued to generate more worrisome conclusions about varenicline. For example, after combing through the FDA MedWatch database, clinical trials, and other published studies, Moore et al²⁰ identified 26 case reports of assault, homicidal ideation, and other aggressive or violent thoughts or acts in varenicline-treated people. The authors noted that many of these events were unprovoked and inexplicable, occurred in people with no history of such behavior, and occurred before the people had stopped smoking. These findings support the idea that varenicline is associated with thoughts and acts of aggression and violence.

Another review by Moore et al,²¹ using the FDA's Adverse Event Reporting System database, also concluded that patients treated with varenicline had a significantly increased risk of depression and suicidal and self-injurious behavior, compared with other smoking-treatment groups and a comparison group of patients receiving antibiotics.²¹ Hays and Ebbert¹⁸ reached a similar conclusion, noting that although varenicline has not been proven to cause serious adverse events such as depression and suicidal behavior, concerns about its safety continue. The findings from our study would seem to add to such concerns. By showing that depression and related symptoms are not expected long-term side effects of smoking cessation, we suggest that varenicline may be responsible.

According to our Clinical Depression variable, 26 of our 70 total patients (37%) had depression. This percentage is right in line with typical estimates of post-stroke depression. For example, in a review, Starkstein and Tranel⁵⁷ reported that about 40% of patients develop depression within the first 2 years after a stroke (also see Robinson et al⁵⁸). So the rate of depression in our neurological patients, most of whom suffered their brain lesions from stroke, are fully in keeping with what would be expected based on the literature. Our patients' smoking status did not seem to make a difference, one way or the other, in their depression outcomes.

Our study had limitations. Perhaps the most obvious is that we studied patients with brain damage. The key controversies about varenicline and psychiatric complications are obviously in persons who do not have brain damage. However, because the demographics of our brain-damaged patients are not unusual, beyond most of them coming from the rural Midwest U.S., we would not expect major limitations in the external validity of our findings. A second limitation is that several of our variables were from self-report measures, and self-report has well-known caveats for assessing mood and psychological status. It was reassuring that our data derived from self-report sources agreed with our data derived from non-self-report sources (clinician observations), so we have no indication of systematic differences as a function of the data source.

Another limitation is that we obtained formal measurements (Beck tests, MMPI-2) only in the chronic epoch. For the acute phase, we characterized our patients' depression based on information gleaned from their medical records, but not with formal psychological tests. In light of our clinical procedures to identify depression and related symptoms in acute patients, though, we are reasonably confident that we did not miss any patients with acute depression. Even so, a prospective study that incorporated formal measurements in the acute epoch would help solidify our conclusions.

One final note of caution is that we obtained our chronic-epoch measurements of depression and related symptoms at different times after lesion onset, ranging from several months to several years. Ideally—and again, this could be addressed in a prospective study—one would obtain all of the relevant measurements at several predetermined points after onset, for example, 6 months, 1 year, and 2 years. Although we do not expect that uniform test scheduling would change our basic conclusions, it is a worthwhile goal for future research.

One important treatment implication of our study concerns the approaches that have been taken over the years to treat tobacco addiction as well as addiction to other substances. Most approaches have been pharmacological, focused on the development of a drug to treat the addiction. However, these treatments can lead to unintended consequences, such as the neuropsychiatric complications associated with varenicline.

In view of evidence that a specific anatomical lesion, in the insula, for example, can lead to smoking cessation^{25, 59, 60} (see Bienkowski et al⁶¹ for a different conclusion) without causing clinically significant neuropsychiatric complications, perhaps it is worth exploring

novel ways to help people quit smoking. Specific brain regions such as the insula could be targeted with noninvasive techniques such as transcranial magnetic stimulation. Deep brain stimulation of the nucleus accumbens has been shown to cause effortless smoking cessation (as well as weight loss).⁶² The insula and the ventral striatum (which contains the nucleus accumbens) are anatomically connected and may well be components of the same neural circuitry. Future research could help uncover the best anatomical target for such a smoking cessation intervention. Although more invasive than transcranial magnetic stimulation, deep brain stimulation probably has the potential to target certain brain structures more selectively, giving it promise in the treatment of refractory smoking addiction.

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TABLE 1

Demographic and Neuropsychological Data of Patients With Brain Lesions, by Smoking Quitters and Non-Quitters

	Quitters (n = 32)	Non-Quitters (n = 38)	P
Age (years) at lesion onset	47.4 ± 14.1	44.8 ± 11.7	0.40
Sex	20 men; 12 women	21 men; 17 women	0.63
Education (years)	13.6 ± 2.5	12.7 ± 2.2	0.54
Handedness (right, left, mixed)	29R, 1L, 2M	33R, 3L, 2M	0.69
No. of patients taking medications: acute epoch	1 antidepressant 0 anti-anxiety	1 antidepressant 1 anti-anxiety	Not tested
No. of patients taking medications: chronic epoch	3 antidepressant 0 anti-anxiety	1 antidepressant 3 anti-anxiety	0.70
Etiology of brain lesion	30 CVA 2 surgical	27 CVA 11 surgical	0.03
WAIS-III VIQ	97.3 ± 15.0	97.2 ± 15.3	0.97
WAIS-III PIQ	97.3 ± 15.0	101.5 ± 13.6	0.24
WAIS-III FSIQ	97.0 ± 13.6	99.6 ± 13.1	0.42
AVLT: Trial 5 (maximum = 15)	9.5 ± 3.0	10.5 ± 2.7	0.14
AVLT: 30-minute recall (maximum = 15)	7.8 ± 4.1	7.5 ± 3.3	0.73
Token Test (maximum = 44)	39.4 ± 9.8	42.2 ± 3.5	0.11
COWA	28.7 ± 15.6	36.3 ± 13.9	0.07
Boston Naming Test (maximum = 60)	46.6 ± 17.5	52.0 ± 10.3	0.12
Facial Discrimination Test (maximum = 54)	43.4 ± 5.4	44.1 ± 4.3	0.54
Trailmaking Test (Part B minus Part A) (sec)	31.0 ± 45.3	50.2 ± 42.2	0.07
WCST: no. of categories achieved (maximum = 6)	5.0 ± 1.8	5.0 ± 1.8	0.94

Data shown as mean ± standard deviation.

No. indicates number; CVA, cerebrovascular accident (stroke); surgical, surgical resection for benign tumor or to treat pharmacoresistant epilepsy; WAIS, Wechsler Adult Intelligence Scale; VIQ, verbal intelligence quotient; PIQ, performance IQ; FSIQ, full scale IQ; AVLT, Auditory-Verbal Learning Test, a measure of word list learning; Token Test, from the Multilingual Aphasia Examination, a measure of aural comprehension; COWA, Controlled Oral Word Association test, a measure of the ability to generate words starting with a given letter; Boston Naming Test, a measure of visual confrontation naming; Facial Discrimination Test, a measure of visuo-perceptual discrimination and matching of unfamiliar faces; Trailmaking Test, a measure of divided attention and response speed; WCST, Wisconsin Card Sorting Test, a measure of concept formation and response monitoring and shifting.

TABLE 2

Depression Outcomes in the Smoking Quitters and Non-Quitters

	Quitters (n = 32)	Non-Quitters (n = 38)	P
Acute Epoch			
Depression Rating Acute	0.25 ± 0.56	0.39 ± 0.64	0.32
Chronic Epoch			
Depression Rating Chronic	0.47 ± 0.76	0.68 ± 0.91	0.29
Clinical Depression	10 ± 31%	16 ± 42%	0.46
BDI-II	10.1 ± 7.8	12.3 ± 9.9	0.40
BDI-II Item 9 (Suicidal Thoughts)	0.13 ± 0.35	0.18 ± 0.47	0.67
BAI	8.5 ± 7.0	13.0 ± 9.8	0.19
MMPI-2 Scale 2	61.9 ± 14.7	62.2 ± 11.3	0.95
MMPI-2 Scale 7	59.8 ± 16.5	58.0 ± 14.5	0.72
MMPI-2 Scale 8	62.4 ± 16.2	60.8 ± 17.6	0.77

Data shown as mean ± standard deviation.

Depression Rating indicates average rating on a 3-point scale ranging from 0 (no depression) to 2 (moderate/severe depression); Clinical depression, number and percentage of patients with depression severe enough to interfere with social, occupational, and other important areas of functioning; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; MMPI-2, Minnesota Multiphasic Personality Inventory-2 (scales are T-scores).

TABLE 3

Depression Outcomes in the Quitters Ease and Quitters Difficulty Groups

	Quitters Ease (n = 16)	Quitters Difficulty (n = 16)
Acute Epoch		
Depression Rating Acute	0.13 ± 0.34	0.38 ± 0.72
Chronic Epoch		
Depression Rating Chronic	0.31 ± 0.70	0.63 ± 0.81
Clinical Depression	3 ± 19%	7 ± 44%
BDI-II BDI-II Item 9 (Suicidal Thoughts)	11.1 ± 6.3 0.00 ± 0	9.3 ± 9.2 0.25 ± 0.46
BAI	7.8 ± 6.2	8.9 ± 7.9
MMPI-2 Scale 2	63.7 ± 16.0	60.8 ± 14.5
MMPI-2 Scale 7	59.3 ± 15.2	60.1 ± 17.9
MMPI-2 Scale 8	61.4 ± 11.9	62.9 ± 18.8

Data shown as mean ± standard deviation.

Depression Rating indicates average rating on a 3-point scale ranging from 0 (no depression) to 2 (moderate/severe depression); Clinical depression, number and percentage of patients with depression severe enough to interfere with social, occupational, and other important areas of functioning; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; MMPI-2, Minnesota Multiphasic Personality Inventory-2 (scales are T-scores).