TITLE: Varenicline for Smoking Cessation in Patients with Psychiatric Illness: A Review of the Risks

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CONTEXT AND POLICY ISSUES:

Smoking is commonly deemed a major cause of lung cancer, cardiovascular disease, peripheral vascular disease, and respiratory disease such as chronic obstructive pulmonary disease.[1] Three million deaths each year are attributed to smoking globally.[1]

Inhaled nicotine is strongly addictive and smoking cessation results in craving and withdrawal symptoms. Even though quitting at any age provides both immediate and long-term health benefits, only a very small portion of smokers (1% to 2%) successfully quit smoking.[1] A variety of methods are available to assist the smokers who attempt to quit, such as counseling with or without pharmacotherapy, pharmacotherapy (including bupropion, nicotine replacement therapy [NRT] and varenicline), hypnosis, and acupuncture.[1,2]

Varenicline is an orally administered, selective nicotinic receptor partial agonist that is indicated for smoking cessation in adults.[1,3] Health Canada approved its use in 2008.[4] Clinical trials have demonstrated that varenicline is superior to placebo, bupropion and NRT in improving the short-term (three months) and long-term (one year) abstinence rates.[1,5] On the other hand, the risks of serious neuropsychiatric symptoms (such as suicidal thoughts and behavior) and self harm in patients treated with varenicline for smoking cessation have also been recognized,[6,7] especially for those with underlying psychiatric illnesses.[8] Studies have examined the safety profile of varenicline in patients with mental illness such as depression, bipolar disorders, and schizophrenia.[3] However, the evidence is limited and results were conflicting regarding the use of varenicline in this subgroup of patients. Varenicline was reported not exacerbate the existing mental illness in some cases and more likely to increase the occurrence of neuropsychiatric adverse events in others. The study authors suggested that the caregivers of such patients should be alerted about the potential neuropsychiatric adverse events that related to the use of varenicline.[3] In the monograph of varenicline in the Compendium of Pharmaceuticals and Specialties (CPS), it states that "*Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms, should be diligently monitored*".[4]

This HTIS report examines the recent evidence on the safety of varenicline for smoking cessation in adult patients with mental illness.

RESEARCH QUESTION:

What is the evidence for the risks of varenicline use for smoking cessation in patients with psychiatric illnesses?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and April 22, 2010. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

From the limited literature search, we identified four observational studies[9-12] that address the research question. No relevant health technology assessments, systematic reviews, randomized controlled trials, or controlled clinical trials were identified about the evidence on safety of varenicline in patients with mental illness.

Observational studies

Philip et al., conducted a perspective study to assess the possible antidepressant effects of varenicline augmentation in patients with existing depressive disorders and nicotine dependence.[9] Eighteen patients were recruited. In this study, it was not clear if the patients attempted to stop smoking. All patients were treated with open-label varenicline in addition to their concomitant therapy for depression. Patients were assessed at baseline and every two weeks for a total of eight weeks, by using a self-report 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR-16), and clinician- and patient-rated Clinical Global Impressions-Severity of Illness (CGI-S) scales. The primary outcome was mean change score on the QIDS-SR-16. Fourteen patients completed this study. An intention-to-treat analysis was performed. The study found a statistically significant improvement in the mean change score on the QIDS-SR-16 between baseline and the end of study (mean ± standard deviation [SD]: 12.9±2.8 vs. 8.2±4.7, $p<0.001$). In this study, "response" was defined as a baseline-to-endpoint ≥ 50% improvement in QIDS-SR-16 score, and "remission" was defined as an endpoint QIDS-SR-16 score ≤ 5; therefore, the differences were not clinically important. Significant improvement in clinician-rated CGI-S score from baseline to the end of study (mean±SD: 3.1±1.1 vs. 2.1±1.4, $p=0.039$) was observed, while no significant changes in patient-rated CGI-S occurred during the study period. A post hoc analysis was performed to examine changes on the specific core QIDS-SR-16 mood and suicidality items. The results showed a significant improvement in core mood score from baseline to end of study (mean±SD: 1.98±0.76 vs. 1.22±0.65, $p<0.001$), but no significant change in suicidality ratings (mean±SD: 0.56±0.71 vs. 0.33±0.59, $p=0.30$). Four patients discontinued due to side effects such as gastrointestinal events and worsened mood/irritability. The authors concluded that varenicline augmentation was associated with

significant improvement in mood in patients with depression; there was no evidence of treatment-related suicidality.

Smith et al. conducted a prospective study to evaluate the effects of varenicline on cognitive function and psychopathology in 14 male patients with schizophrenia.[10] All patients were long-term smokers, and most of them did not have a strong desire to definitely stop smoking. Varenicline was prescribed for nine weeks. Patients were on stable antipsychotic medications as well. The following tools were used for neuropsychological testing and psychiatric assessments at baseline and during the treatment with varenicline: the RBANS battery, a short test battery which has been standardized and used extensively with schizophrenic patients; the Virtual Morris Water Maze Task (MWT), to evaluate visual learning and memory deficits in schizophrenia patients; and the PANSS scale, to evaluate the presence/absence and severity of positive, negative and general psychopathology of schizophrenia. Eleven patients with schizophrenia from another study in the same institution who did not receive varenicline were used as a control group. Twelve of the 14 patients treated with varenicline completed the study. From baseline to the end of treatment, varenicline produced significant improvements in some cognitive test scores which were primarily associated with verbal learning and memory (mean±SD for RBANS list learning score: 15.75±5.50 vs. 19.50±4.19, p=0.005; mean±SD for RBANS list recall score: 1.92±1.83 vs. 3.33±1.37, p=0.025; mean±SD for RBANS language index: 70.17±13.23 vs. 83.50±12.55, p=0.003; mean±SD for MWT latency to find the target: 47.27±13.69 seconds vs. 43.75±12.77 seconds, p=0.031). The improvement on MWT was observed in only four patients. For the psychiatric assessments, no patient showed a clinically significant increase in PANSS scores during the treatment with varenicline, or developed suicidal ideation or signs of clinical depression. There were no significant differences in baseline PANSS scores between the two groups or in the change in PANSS scores over time. The commonly reported side effects in this study were nausea, vomiting, shaking, dry mouth, tiredness-sleepiness and cramps. Two patients treated with varenicline withdrew in the first two weeks of the study because of nausea or shaking. The authors concluded that varenicline may have some beneficial cognitive effects, and it may not increase psychopathology or depression in most patients with schizophrenia; however, these have to be confirmed in larger studies.

McClure et al. compared the effects of varenicline on mood and self-reported symptoms commonly associated with varenicline use among smokers with and without probable lifetime depression, using data from a randomized controlled trial (COMPASS).[11] The purpose of COMPASS was to compare the effectiveness of three behavioral programs for smoking cessation: phone-base counseling, web-based intervention, or combined phone and web-based intervention. All patients received varenicline for three months. No details of the use of antidepressants were provided. The evaluation was performed at baseline, 21 days post-target quit date, and three months past-target quit date. A diagnosis of depression was based on depression history, which was assessed using an item reflecting the two featured symptoms of major depression in the Diagnostic and Statistical Manual of Mental Disorders IV, and current depressive symptoms, which was assessed using a brief measure derived from the Hopkins Symptom Checklist. Higher higher scores on the Hopkins Symptom Checklist indicate greater depressive symptoms. In the 1,117 patients included in this study, 56.2% (661/1,117) had a diagnosis of major depression (DH+). Compared to the DH- group, these patients were more likely to be older, female, white, and unmarried. At 21 days, DH+ participants were more likely to intentionally take fewer tablets of varenicline in a day than prescribed. The mean depression scores were higher among DH+ participants at baseline and declined among both DH groups

over time. After controlling for the potential confounders such as gender, marital status, age, race and behavioral treatments, the adjusted mean change in depression score was greater for the DH- group at 21 days (-0.19 in DH+ vs. -0.33 in DH-, p<0.001) and three months (-0.22 in DH+ vs. -0.32 in DH-, p=0.02). There were no differences between the DH+ and DH- groups with respect to the proportion of patients whose depressive symptom scores worsened from baseline to follow up. The DH+ participants were more likely to report side effects of tension/agitation (p=0.02), irritability/anger (p=0.009), depression (p<0.001), difficulty concentrating (p=0.005) and confusion (p<0.001) at 21 days; at three months, the DH+ group had higher rates of anxiety (p=0.002) and depression (p<0.001). This study found that smokers with a probable lifetime history of depression were more likely to report a number of neuropsychiatric side effects after initiating varenicline treatment including tension/agitation, irritability/anger, depression, difficulty concentrating, and confusion; yet the data do not indicate these patients were more likely to experience new or significantly worse mood disturbance compared to DH- patients.

Stapleton et al. conducted a study to compare the effectiveness of varenicline with NRT for smoking cessation and to evaluate the safety of varenicline in people with mental illness.[12] Eligible patients participated in seven group support sessions over six weeks with either varenicline (n=208) or NRT (n=204). Patient received varenicline or NRT for 12 weeks. The self-completion tobacco withdrawal symptoms scale consisted of seven known symptoms (depression, irritability, restlessness, difficulty concentrating, difficulty stopping smoking, urges to smoke, and strength of urges to smoke), with higher scores indicating more severe symptoms. The baseline patient characteristics in the varenicline and NRT groups were similar with respect to demographics, health history and smoking characteristics. In the varenicline group, 25.5% (53/208) had a current mental health disorder, such as depression, bipolar disorder, psychosis or eating disorder. The authors stated that there was no evidence that patients with mental illness experienced more adverse symptoms, and no evidence symptoms of mental illness were exacerbated by varenicline, without providing detailed data. The authors concluded that varenicline is equally effective and safe in those with and without a mental illness.

Limitations

- There were no health technology assessments, systematic reviews, randomized controlled trials, or controlled clinical trials evaluating the safety profile of varenicline in adults with mental illness for smoking cessation.
- There were a limited number of observational studies available.
- Some studies did not indicate if the patients had a desire to stop smoking. This might impact the generalizability of the results to individuals with mental illness who are trying to quit.
- The longest treatment duration of varenicline was 12 weeks; therefore the long-term impact of this drug on psychiatric symptoms remains unclear.
- Study quality of the included observational studies was low due to the potential for various biases (i.e. selection bias) associated with the study design and sample size. This suggests that their results should be interpreted with caution.
- Authors of all included studies received financial support from the pharmaceutical industry.

- The severity of the symptoms was evaluated with different tools, which makes it difficult to compare between studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Varenicline is an effective smoking cessation aid.[13] Due to the concern of its potential for adverse effects on patients with existing mental illness, we conducted a rapid review of the evidence of safety data of varenicline in this patient population.

In total four observational studies provided evidence to address the research question. The numbers of patients with mental illnesses in each study ranged from 14 to 661. Patients took varenicline for eight to 12 weeks and also received other therapies such as behavioral treatment programs, antidepressants or other medications for concomitant mental illness. A variety of assessment tools were adopted to investigate the change in psychiatric symptoms, cognitive functions, and suicidality.

In patients with depression, the depressive symptoms improved after treatment with varenicline, and there was no evidence of new/worsened mood disturbance or suicidality related to varenicline. In patients with schizophrenia, some benefits for verbal learning and memory were observed after the use of varenicline. No suicidal ideation was reported to be related to varenicline. In a population mixed with depression, bipolar disorder and psychosis, no evidence was found that patients experienced more adverse symptoms or varenicline worsened the existing mental illness, compared to those without a mental illness.

The data were sparse and the quality of the included studies was low due to the sample size and design. Based on the studies included in this rapid review, there is no compelling evidence to justify the safety concerns of varenicline for smoking cessation in patients with mental illness. It remains unclear whether the improvement in psychiatric symptoms is related to the use of varenicline, or the use of concomitant medications. Further well-designed clinical studies would provide more rigorous evidence to fill the gap.

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