Smoking cessation: Varenicline and the risk of neuropsychiatric adverse events

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Mr. T, age 34, is a veteran who recently returned to civilian life. He presents to his local Veteran Affairs facility for transition of care. During active duty, he had been diagnosed with obstructive sleep apnea, tobacco use disorder, posttraumatic stress disorder (PTSD) secondary to combat exposure, and insomnia. Mr. T says he wants to quit smoking; currently, he smokes 2 packs of cigarettes per day. The primary care clinician notes that Mr. T has uncontrolled PTSD symptoms and poor sleep, and refers him for an outpatient mental health appointment.

At the mental health appointment 3 weeks later, Mr. T asks about medications to quit smoking, specifically varenicline (***Table 1***,[1] ***page 42***). Mr. T's PTSD Checklist for DSM-5 score is 52, which indicates severe PTSD symptomatology. He says he sees shadowy figures in his periphery every day, and worries they are spying on him. His wife reports Mr. T has had these symptoms for most of their 10-year marriage but has never been treated for them. After a discussion with the outpatient team, Mr. T says he is willing to engage in exposure therapy for PTSD, but he does not want to take any medications other than varenicline for smoking cessation.

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Cigarette smoke is a known carcinogen and risk factor for the development of cardiovascular and respiratory diseases and other comorbidities. People with severe mental illness (SMI) are 3 to 5 times more likely to smoke, and they often face multiple barriers to cessation, including low socioeconomic status and lack of support.[2] Even when patients with SMI are provided appropriate behavioral and pharmacologic interventions, they often require more frequent monitoring and counseling, receive a longer duration of drug therapy, and experience lower smoking cessation rates than the general population.[2]

Current guidelines recommend nicotine replacement therapy (NRT), bupropion, varenicline, and behavioral support as first-line therapies for smoking cessation in patients with and without SMI.[2] Evidence suggests that varenicline is more effective than other pharmacologic options; however, in 2009 a black-box warning was added to both varenicline and bupropion to highlight an

Practice Points

- **Smoking cessation should be discussed with and offered to all patients.** Pharmacotherapy should be selected based on proven efficacy, safety, and patient-specific factors.
- **Varenicline is a safe and effective first-line option** for patients with psychiatric illness that is controlled.
- Patients with severe mental illness who are prescribed varenicline **should be educated on the risks and closely monitored.**

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Table 1

Varenicline: An overview

Mechanism of action	Dosage strategies
Alpha(4)beta(2) nicotinic receptor agonist, prevents nicotine binding	Titrated regimen: 0.5 mg/d from Day 1 to Day 3, increase to 0.5 mg twice daily from Day 4 to Day 7, increase to 1 mg twice daily on Day 8 and beyond Patient may quit smoking on Day 8 (fixed quit date), between Day 8 and Day 35 (flexible quit date), or gradually reduce tobacco use over several weeks (ie, 50% reduction by Week 4, additional 50% reduction by Week 8, abstinence by Week 12)

Source: Reference 1

Table 2

Varenicline trials and neuropsychiatric adverse events

Study	Population	Design	Intervention
Anthenelli et al[3]	Treatment-seeking participants age 18 to 75 who did and did not meet DSM-IV criteria for psychiatric disorders, smoked >10 cigarettes/d, and had CO concentration >10 ppm	Double-blind, triple-dummy, placebo- and active-controlled, randomized controlled trial	1:1:1:1 ratio of nicotine patch, varenicline, bupropion, and placebo for 12 weeks followed by 12-week nontreatment phase
Beard et al[4]	Treatment-seeking participants age 18 to 75 who did and did not meet DSM-IV criteria for psychiatric disorders, smoked >10 cigarettes/d, and had CO concentration >10 ppm	Secondary, post-hoc analysis of EAGLES	
Ayers et al[5]	Subgroup of EAGLES participants diagnosed with GAD (N = 243), PTSD (N = 192), and panic disorder (N = 277), compared to nonpsychiatric cohort (N = 4,028)	Secondary, post-hoc analysis of EAGLES	
Evins et al[6]	Treatment-seeking participants age 18 to 70 with schizophrenia, schizoaffective disorder, or bipolar disorder, smoked ≥10 cigarettes/d for ≥1 year, and had CO concentration ≥9 ppm	Randomized, double-blind, placebo-controlled, parallel-group, relapse prevention trial	Eighty-seven of 203 participants met criteria to enter double-blind, relapse-prevention phase after 12 weeks of open-label varenicline therapy. CBT and varenicline vs placebo from Week 12 to Week 52

CBT: cognitive-behavioral therapy; GAD: generalized anxiety disorder; NPSAEs: neuropsychiatric adverse events; OCD: obsessive-compulsive disorder; OR: odds ratio; PTSD: posttraumatic stress disorder

Clinical Point

First-line treatments for smoking cessation include nicotine replacement therapy, bupropion, and varenicline

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increased risk of neuropsychiatric events in individuals with SMI.[2] This led some clinicians to hesitate to prescribe varenicline or bupropion to patients with psychiatric illness. However, in 2016, the EAGLES trial evaluated the safety of varenicline, bupropion, and NRT in smokers with and without psychiatric disorders, and based on the findings, the black-box warning was removed.[2]

This article reviews the evidence regarding the use of varenicline and the risk of neuropsychiatric adverse events in patients with psychiatric illness. ***Table 2***[3-6] provides a summary of each varenicline trial we discuss.

Adverse effects	Warnings	Pharmacokinetics
Nausea, vomiting, constipation, flatulence, abnormal dreams, insomnia, headache, irritability	Reduced alcohol tolerance, serious skin reactions, dose-dependent nausea, seizures, renal dosing	High oral bioavailability, T_{max} approximately 3 to 4 hours, 92% excreted unchanged in urine

Outcome(s)	Results	Notes
Composite measure of moderate to severe NPSAEs	No difference in rate of moderate to severe NPSAEs in varenicline group in the psychiatric cohort (N = 1,026) vs other treatment arms (N = 3,048) in the psychiatrist cohort	All participants received smoking cessation counseling during follow-up; patients were required to be psychiatrically stable at enrollment
Aimed to test hypothesis of EAGLES trial more directly using Bayes factor	Bayes factor of 0.52 and 0.71 for varenicline and bupropion, respectively, which suggests no increase in NPSAEs associated with either medication vs placebo	Bayes factor expresses ratio of the odds of 2 hypotheses being correct in a data set; values <1/3 support null hypothesis; values >3 support experimental hypothesis; values in between may be insensitive
Moderate to severe NPSAEs; abstinence rates during treatment (Week 9 to Week 12) and follow-up (Week 9 to Week 24); 7-day point prevalence abstinence at end of treatment	Incidence of NPSAE ranged from 5.4% to 6.9% in anxiety cohort compared to 2.1% in the nonpsychiatric cohort. No NPSAE differences in anxiety cohort based on treatment group; no frank interaction between anxiety diagnosis and treatment response	Participants with OCD (N = 27) and social phobia disorder (N = 48) were not included in analysis due to sample size
Primary outcome was 7-day continuous abstinence rates at Week 52 (biochemically confirmed)	Higher rate of continuous abstinence in extended-duration varenicline group vs placebo (60% vs 19%, OR 6.2; 95% CI, 2.2 to 19.2). No significant treatment effect differences on psychiatric symptom ratings or adverse drug reactions	Participants were required to be on a stable dose of an antipsychotic or mood stabilizer for ≥30 days before enrollment. Participants also received weekly CBT during the open-label phase

Clinical Point

Varenicline's black-box warning regarding the risk of neuropsychiatric events was removed

The EAGLES trial

EAGLES was a multicenter, multinational, randomized, double-blind, triple-dummy, placebo- and active-controlled trial of 8,144 individuals who received treatment for smoking cessation.[3] The primary endpoint was the incidence of a composite measure of moderate to severe neuropsychiatric events (NPSAEs).[3] Participants were split into psychiatric (N = 4,116) and nonpsychiatric (N = 4,028) cohorts and randomized into 4 treatment arms: varenicline 1 mg twice a day, bupropion 150 mg twice a day, nicotine patch 21 mg/d with taper, or placebo, all for 12 weeks with an additional 12 weeks of follow-up. All participants smoked ≥10

cigarettes per day. Individuals in the psychiatric cohort had to be psychiatrically stable (no exacerbations for 6 months and stable treatment for 3 months). Exclusionary diagnoses included psychotic disorders (except schizophrenia and schizoaffective disorder), dementia, substance use (except nicotine), and personality disorders (except borderline personality disorder).[2]

The rates of moderate to severe NPSAEs in the varenicline groups were 1.25% (95% CI, 0.60 to 1.90) in the nonpsychiatric cohort and 6.42% (95% CI, 4.91 to 7.93) in the psychiatric cohort.[3] However, when comparing the varenicline group of the psychiatric cohort to the other arms of the psychiatric cohort, there were no differences (bupropion 6.62% [95% CI, 5.09 to 8.15], nicotine patch 5.20% [95% CI, 3.84 to 6.56], placebo 4.83% [95% CI, 3.51 to 6.16], respectively). The primary efficacy endpoint was continuous abstinence rates (CAR) for Week 9 through Week 12. In the psychiatric cohort, varenicline was superior compared to placebo (odds ratio [OR] 3.24; 95% CI, 2.56 to 4.11), bupropion (OR 1.74; 95% CI, 1.41 to 2.14), and nicotine patch (OR 1.62; 95% CI, 1.32 to 1.99).[3]

Further analysis of EAGLES

Beard et al[4] used Bayes factor testing for additional analysis of EAGLES data to determine whether the data were insensitive to neuropsychiatric effects secondary to a lack of statistical power. In the psychiatric cohort, the varenicline and bupropion groups exhibited suggestive but not conclusive data that there was no increase in NPSAEs compared to placebo (Bayes factor 0.52 and 0.71, respectively).[4]

Another EAGLES analysis by Ayers et al[5] evaluated participants with anxiety disorders (N = 712), including PTSD (N = 192), generalized anxiety disorder (GAD) (N = 243), and panic disorder (N = 277). Of those with PTSD who received varenicline, there were no statistically significant differences in CAR from Week 9 to Week 12 vs placebo.[5] However, there was a significant difference in individuals with GAD (OR 4.53; 95% CI, 1.20 to 17.10), and panic disorder (OR 8.49; 95% CI, 1.57 to 45.78).[5] In contrast to CAR from Week 9 to Week 12, 7-day point prevalence abstinence at Week 12 for participants with PTSD was significant (OR 4.04; 95% CI, 1.39 to 11.74) when comparing varenicline to placebo. Within the anxiety disorder cohort, there were no significant differences in moderate to severe NPSAE rates based on treatment group. Calculated risk differences comparing varenicline to placebo were: PTSD group -7.73 (95% CI, -21.95 to 6.49), GAD group 2.80 (95% CI, -6.63 to 12.23), and panic disorder group -0.18 (95% CI, -9.57 to 9.21).[5]

Other studies

Evins et al[6] conducted a randomized controlled trial to evaluate the safety of varenicline maintenance therapy in patients with schizophrenia or bipolar disorder. To be deemed clinically stable, participants in this study needed to be taking a stable dose of an antipsychotic or mood-stabilizing agent(s) for ≥30 days, compared to the 3-month requirement of the EAGLES trial.[3,6] Participants received 12 weeks of open-label varenicline; those who achieved abstinence (N = 87) entered the relapse-prevention phase and were randomized to varenicline 1 mg twice a day or placebo for 40 weeks. Of those who entered relapse-prevention, 5 in the placebo group and 2 in the varenicline group were psychiatrically hospitalized (risk ratio 0.45; 95% CI, 0.04 to 2.9).[6] These researchers concluded that varenicline maintenance therapy prolonged abstinence rates with no significant increase in neuropsychiatric events.[6]

Although treatment options for smoking cessation have advanced, individuals with SMI are still disproportionately affected by the negative outcomes of cigarette smoking. Current literature suggests that varenicline does not confer an appreciable risk of neuropsychiatric events in otherwise stable patients and is the preferred first-line treatment. However, there is a gap in understanding the impact of this medication on individuals with unstable psychiatric

Clinical Point

Research suggests that varenicline does not confer an appreciable risk of neuropsychiatric events in otherwise stable patients

illness. Health care professionals should be encouraged to use varenicline with careful monitoring for appropriate patients with psychiatric disorders as a standard of care to help them quit smoking.

CASE CONTINUED

After consulting with the psychiatric pharmacist and discussing the risks and benefits of varenicline, Mr. T is started on the appropriate titration schedule (***Table 1,***[1] ***page 42***). A pharmacist provides varenicline education, including the possibility of psychiatric adverse effects, and tells Mr. T to report any worsening psychiatric symptoms. Mr. T is scheduled for frequent follow-up visits to monitor possible adverse effects and his tobacco use. He says he understands the potential adverse effects of varenicline and agrees to frequent follow-up appointments while taking it.

Related Resources

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Drug Brand Names

Bupropion • Wellbutrin
Varenicline • Chantix

Clinical Point

More research is needed on varenicline's impact on patients with unstable psychiatric illness

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