

What is the incidence of seizure risk for patients using Chantix® or Zyban®?

Background

Bupropion sustained-release (SR, Zyban®) is a Food and Drug Administration (FDA)- approved drug for aiding patients with smoking cessation.¹ Bupropion was initially approved in 1985 as an antidepressant, then received approval in 1997 as a smoking cessation aid. Although the exact mechanism of action for its effects on smoking cessation is not known, bupropion is thought to be a weak central inhibitor of both norepinephrine and dopamine reuptake. For smoking cessation, bupropion should be initiated 1 week before the patient's targeted quit date, titrated slowly starting at 150 mg once daily for 3 days, then increased to the maintenance dosage of 150 mg twice daily (300 mg total per day). The manufacturer requires titration and a maximum daily dosage in order to decrease the risk of seizures. In the label, the manufacturer reports that the seizure incidence is directly linked to the dosage of bupropion, with approximately 0.1% in depressed patients taking up to 300 mg of bupropion SR daily, and 0.4% in depressed patients taking up to 400 mg of bupropion SR daily.

Varenicline (Chantix®) obtained FDA approval in 2006, also as a smoking cessation aid.² Varenicline is a central nicotinic receptor partial agonist that binds the receptors with such a high affinity that it prevents administered nicotine from fully activating the receptor. Dosing of varenicline also requires titration upon initiation, 1 week before the targeted quit date, with 0.5 mg given orally once daily on days 1-3, 0.5 mg twice daily on days 4-7, and 1 mg twice daily for weeks 2-12. An additional 12 weeks of therapy at the maintenance dose may be required to help achieve long-term smoking cessation.

Risk of Seizures with Varenicline

A search of Embase and the FDA website was performed to identify studies on the risk of seizures with varenicline. A retrospective case-control study was identified, examining the risk of seizures with varenicline use, as well as a safety report from the Australian Therapeutic Goods Administration (TGA).^{3,4} An FDA safety review regarding the development of seizures and other safety concerns in patients who used varenicline was also retrieved.⁵

The Australian TGA reviewed adverse events that had been submitted by prescribers relating to the use of varenicline and issued a safety bulletin in 2008 regarding potential neuropsychiatric events and incidence of seizures.⁴ A total of 210,000 prescriptions for varenicline had been filled in Australia at that time, and a total of 15 reports of seizure had been submitted to the adverse reactions advisory committee. No patient data were included in the analysis, so there was no way to determine whether any of these seizures were related to established seizure disorders or new in onset. Regardless, the TGA advised prescribers to be cautious when prescribing varenicline in patients with prior seizure disorders.

In March 2015, the FDA issued a drug safety communication on varenicline with respect to reported neuropsychiatric events and seizures.⁵ The FDA searched published literature for any reports of seizures with varenicline and reviewed the FDA Adverse Events Reporting System (FAERS). They identified 64 cases of seizures. Median time to onset of seizure was 2 to 3 weeks following initiation of varenicline (data reported in approximately 60% of cases). Thirty-seven cases involved patients with no prior history of seizure disorders, and 27 involved patients who had a history of controlled seizures. Of the 37 cases involving those with no prior history, 10 had no reported contributing factors other than varenicline. Contributing factors, such as concurrent use of other medications which can lower the seizure threshold, were identified in the remaining 27 cases.

Most recently, a nested case-control study was published (in abstract-form), which quantified the risk of seizure in patients using varenicline for smoking cessation.³ The primary outcome of the study was to establish the risk of seizure outcomes associated with varenicline use. They performed a search of the IMS LifeLink database for international classification of diseases codes – ninth revision, clinical modification (ICD-9-CM) relating to seizure disorders, as well as prescriber orders for electroencephalograms, over the timeframe of 2008 to 2013. The nest used for the study was defined as patients who made an attempt to quit smoking and who did not have a seizure for 12 months. Incident cases were those who attempted to quit smoking and had a presumptive seizure. Cases and controls were then matched based on age, sex, and entry date, then compared for varenicline usage within the previous 3 months. In total, 838 case-control pairs were analyzed. The likelihood of a patient having a seizure versus no seizure within 3 months of receiving a varenicline prescription was determined to be significant (unadjusted odds ratio [OR] 1.57, 95% confidence interval [CI] 1.124 to 2.197). After adjusting for covariates, the authors still found the results to be statistically significant (adjusted OR 2.23; 95% CI 1.485 to 3.336).

Risk of Seizures with Bupropion

A search of Embase and the FDA website was performed for references relating to seizures and bupropion, including Cochrane reviews and meta-analyses. A total of 152 studies were found, with 2 of the most recent publications being included in this summary.^{6,7}

In 2007, Alper et al conducted a review of phase II and phase III clinical trials to determine the effect of psychopharmacological agents and psychiatric disorders on seizure threshold.⁶ The authors retrieved all submitted phase II and phase III clinical trial data submitted to the FDA from 1985 to 2004 for a wide range of psychoactive drugs, broadly including (then) new drugs of the antianxiety, antipsychotic, and antidepressant classes, including bupropion. The primary aim of the study was to analyze incidence of seizures reported in the clinical trials, for both the treatment groups and placebo groups. The secondary aim of the study was to find evidence for any risk factors for seizures associated with different psychiatric disorders. Seizure incidence rates for the drugs were determined for each drug from the available data; comparing these to the general population incidence rate for seizures, standardized incidence ratios (SIR) for the drugs were determined.

From the clinical trials that lead to approvals of 20 different drugs, including bupropion immediate-release (IR) and bupropion SR, data for a total of 75,873 patients were analyzed.⁶ Bupropion IR was found to have a significantly higher seizure incidence rate of 0.6% compared to bupropion SR with a seizure incidence rate of 0.1% ($p < 0.001$). The authors reported bupropion IR was the only drug studied which had a significantly increased SIR at 1.58 (95% CI 1.03 to 2.32). An individual analysis of bupropion SR was not reported, but antidepressants as a class had an SIR of 0.48 (95% CI 0.36 to 0.61) and antidepressants as a class excluding bupropion IR had an SIR of 0.31 (95% CI 0.21 to 0.43). The authors discussed the potential importance of the lower bupropion maximum dosage for bupropion SR (400 mg/d) to bupropion IR (450 mg/d), as well as the fact that the bupropion SR, by design, does not have the same peak concentrations as the IR form.

In 2016, a Cochrane review was performed by Hughes et al examining the usage of antidepressants for smoking cessation.⁷ The purpose of the review was to examine the efficacy and safety profiles of multiple antidepressant medications, including bupropion, in assisting with long-term smoking cessation. Controlled clinical trials were selected where the medication was compared to placebo or an active control for achieving long-term smoking cessation. Trials must have demonstrated efficacy through either

smoking abstinence for 6 months, or a reduction of greater than 50% of cigarettes smoked per day for 6 months. Safety profiles were analyzed using reported adverse events or number of study dropouts due to adverse events. In total, 90 clinical trials were included in this review, with 65 studies including bupropion. Of those trials, 60% had a follow-up period of 12 months, and the remaining 40% had a follow-up period of 6 months. These studies had a combined patient population of over 13,000 people (total not specified). From the reported adverse events in all of these trials, 10 patients had reported seizures – an incidence of approximately 0.077%. This number appears to be roughly in line with the incidence reported in the FDA label (0.1 to 0.4%).

Discussion and Summary

With respect to varenicline, there appears to be limited evidence linking seizures and varenicline usage. Most of the data are derived from adverse reactions reported to regulatory bodies such as the FDA and its Australian equivalent, the TGA.^{4,5} The reports published by these agencies indicate that, given the limited data, it would be prudent to be cautious when prescribing varenicline to patients with a prior history of seizures. The recent observational study by Chopra et al seems to indicate that the risk of seizures from varenicline usage is significant, though given the study design and population size, further research should be conducted to ascertain the true population risk.³

For bupropion, the link between seizures and usage of the medication has been known for some time and well documented.^{1,6,7} It is also accepted that the risk of seizures is dose-dependent with higher doses associated with a higher risk. Multiple meta-analyses have been conducted that report the incidence of seizure with bupropion use, among other medications. Though varying incidences have been reported, the rate of seizures with bupropion appears to be low.

References

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