

FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings

This is an update to the [Drug Safety Communication](#) issued on March 9, 2015.

Safety Announcement

[12-16-2016] Based on a U.S. Food and Drug Administration (FDA) review of a large clinical trial that we required the drug companies to conduct,¹ we have determined the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion)^{*} is lower than previously suspected. The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past. However, most people who had these side effects did not have serious consequences such as hospitalization. The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines.

As a result of our review of the large clinical trial, we are removing the *Boxed Warning*, FDA's most prominent warning, for serious mental health side effects from the Chantix drug label. The language describing the serious mental health side effects seen in patients quitting smoking will also be removed from the *Boxed Warning* in the Zyban label.[†] We are also updating the existing warning section in both labels that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial. This decision is consistent with the recommendations of external experts at a September 2016 [FDA Advisory Committee meeting](#). The patient Medication Guide that explains the risks associated with the use of the medicines will continue to be provided with every patient prescription; however, the risk evaluation and mitigation strategy (REMS) that formally required the Medication Guide will be removed.

Our review of the clinical trial results also confirmed that Chantix, Zyban, and nicotine replacement patches were all more effective for helping people quit smoking than was an inactive treatment called a placebo. These medicines were found to better help people quit smoking regardless of whether or not they had a history of mental illness.

The health benefits of [quitting smoking](#) are substantial, including decreasing the chances of developing lung disease, heart disease, and some cancers. There are also benefits that are nearly immediate or occur after a short time as a nonsmoker such as improvements in circulation, breathing, and the senses of taste and smell.² Millions of Americans have serious health problems caused by smoking that can be reduced by quitting. Smoking has been found to harm many organs in the body and diminishes a person's overall health. Chantix and Zyban are prescription medicines that are FDA-approved to help adults quit smoking.

Health care professionals should counsel patients about the benefits of stopping smoking and how they can get help to quit, and discuss the benefits and risks of using medicines to help them quit smoking.

Patients should stop taking Chantix or Zyban and call their health care professionals right away if they notice any side effects on mood, behavior, or thinking. Patients should also talk to their health care professionals for help and information about stopping smoking, including about whether stop-smoking medicines may help or if they have any questions or concerns about taking a medicine (See Related Information for more quit smoking resources).

FDA continues to evaluate the safety and effectiveness of drugs after they go on the market. In the case of Chantix and Zyban, we received and assessed case reports of serious changes in mood and behavior in patients taking the medicines, which led us to require that a *Boxed Warning* be added to the labels in 2009. At the time, we required the drug companies to conduct a large clinical trial to evaluate these side effects, and we have now reviewed the findings (see Data Summary).¹ Based on these results, we now have a better idea about the frequency and severity of these side effects on mood, behavior, or thinking, and have confirmed that the benefits of taking Chantix or Zyban to help quit smoking outweigh these risks.

We previously communicated about this issue in [2009](#), [2011](#), and [2015](#). The clinical trial results were discussed at an [FDA Advisory Committee meeting](#) on September 14, 2016.

We urge patients and health care professionals to report side effects involving Chantix, Zyban, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*There are other bupropion products that are approved for psychiatric disorders, including major depressive disorder. The language concerning serious side effects on mood, behavior, or thinking in people taking bupropion for stopping smoking will be removed from the *Boxed Warning* of those products' labels as well.

†The active ingredient in Zyban is in the antidepressant class; therefore the label carries the class *Boxed Warning* for suicidality and antidepressant drugs. This language will remain in a *Boxed Warning* in the labels for Zyban and other bupropion products.

Additional Information for Patients

- FDA's review of a large clinical trial that we required drug companies to conduct has found that the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) is lower than previously suspected.¹
- However, when trying to quit smoking with or without stop-smoking medicines, some people have significant side effects including new or worsening mental health problems such as changes in behavior or thinking, hostility, agitation, depressed mood, or suicidal thoughts or actions. These symptoms happen more often in people who had a history of mental health problems before trying to quit smoking than in people without a history of mental health problems.
- Based on the results of the clinical trial, we have a better idea about the frequency and severity of these side effects, and we have confirmed that the benefits of taking Chantix or Zyban to help quit smoking outweigh the risk of these side effects on mood, behavior, or thinking.
- Stop taking Chantix or Zyban and call your health care professional right away if you, your family, or your caregiver notices any of these side effects. Work with your health care professional to decide whether you should continue to take Chantix or Zyban. In many people, these side effects went away after stopping the medicine, but in some people they continued. It is important for you to follow-up with your health care professional until your side effects go away.
- The health benefits of quitting smoking are immediate and substantial. Smoking has been found to harm many organs in the body and diminishes a person's overall health.
- Soon after quitting, circulation and blood pressure improve, the senses of taste and smell return, and it becomes easier to breathe. In the longer term, quitting smoking can decrease the chances of developing lung disease, heart disease, and some cancers.
- By quitting smoking, smokers can also help prevent heart disease and lung cancer in people exposed to second-hand smoke.
- More information about quitting smoking can be found on the [National Cancer Institute's website](#).
- Chantix works by blocking the effects of nicotine from smoking on the brain, and Zyban works by altering the level of some chemicals in the brain, which may relieve the withdrawal symptoms that occur when stopping smoking.
- Talk to your health care professional if you have any questions or concerns about quitting smoking or taking Chantix or Zyban.
- Read the patient [Medication Guide](#) that comes with each new Chantix or Zyban prescription because the information may have changed. The Medication Guide explains the risks associated with the use of the medicine.
- Report side effects from Chantix, Zyban, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA required the manufacturers of Chantix (varenicline) and Zyban (bupropion), Pfizer Inc. and GlaxoSmithKline respectively, to conduct a clinical trial to evaluate the neuropsychiatric safety of Chantix and Zyban for smoking cessation in patients without and with a history of psychiatric disorders.¹ The trial was a 24-week, double-blind, active- and placebo-controlled, multi-center, parallel group trial designed to assess the safety and efficacy of Chantix 1 mg twice daily and Zyban 150 mg twice daily for smoking cessation. Nicotine replacement therapy (NRT) was included as an active control. The duration of active treatment was 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks. Patients were classified into one of two cohorts—those without a diagnosis of a psychiatric disorder and those with an established and stable diagnosis of psychiatric disorder confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening. An equal number of patients without or with a diagnosis of a psychiatric disorder were enrolled and randomized among the four treatment arms in a 1:1:1:1 ratio.

The trial enrolled 8,144 patients at 140 centers in 16 countries, including the U.S., of which 8,058 patients were randomized to Chantix (n=2,016), Zyban (n=2,006), NRT (n=2,022), and placebo (n=2,014). Among the 4,074 patients in the psychiatric history cohort, approximately 70 percent had affective disorders, 19 percent had anxiety disorders, 9 percent had psychotic disorders, and less than 1 percent had borderline personality disorder.

As shown in Table 1 below, clinically significant neuropsychiatric adverse effects occurred at a similar frequency of about 3 percent across treatment groups in patients without psychiatric diagnoses. In the cohort of patients with psychiatric diagnoses, there was a higher incidence across groups, and a numerically increased risk associated with Chantix and with Zyban (approximately 12 percent), compared to placebo (approximately 10 percent). There was no meaningful difference in risk between Chantix and Zyban (see Table 1).

Table 1. Incidence of Clinically Significant Neuropsychiatric Adverse Events

	Chantix 1 mg BID*	Zyban 150 mg BID*	NRT 21 mg/day with taper	Placebo
Non-psychiatric cohort	3.1%	3.5%	3.3%	4.1%
Psychiatric cohort	12.2%	11.8%	9.8%	9.5%

*BID=twice daily

Serious adverse events (i.e., events of a life-threatening nature, or resulting in hospitalization or death) in the psychiatric history cohort primarily involved psychiatric decompensation. Other reported events had an impact on patient functioning; however, most events were not serious (as defined above) and were usually transient.

The trial evaluated efficacy by comparing smoking abstinence rates of Chantix and Zyban relative to placebo for the last 4 weeks of the 12-week treatment and continuously through Week 24, as measured by carbon monoxide (CO)-confirmed continuous abstinence rate. In both cohorts, patients treated with Chantix, Zyban, or nicotine patch (NRT) had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and weeks 9 through 24 compared to patients treated with placebo (see Table 2).

Table 2. Continuous Abstinence (95% Confidence Interval)

	Chantix 1 mg BID	Zyban 150 mg BID	NRT 21 mg/day with taper	Placebo
Weeks 9 through 12				
Non-psychiatric cohort	38% (35%, 41%)	26% (23%, 29%)	26% (24%, 29%)	14% (12%, 16%)
Psychiatric cohort	29% (26%, 32%)	19% (17%, 22%)	20% (18%, 23%)	11% (10%, 14%)
Weeks 9 through 24				
Non-psychiatric cohort	25% (23%, 28%)	19% (16%, 21%)	18% (16%, 21%)	11% (9%, 13%)
Psychiatric cohort	18% (16%, 21%)	14% (12%, 16%)	13% (11%, 15%)	8% (7%, 10%)

Although there is still a risk of neuropsychiatric adverse events with Chantix and Zyban, most people who had changes in mood, behavior, or thinking did not have serious consequences such as hospitalization. Therefore, we believe this trial confirms that the benefits of taking these drugs for smoking cessation outweigh the risk of neuropsychiatric adverse events, which appears to be lower than previously suspected.

References

1. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-20.
2. National Cancer Institute. Harms of Cigarette Smoking and Health Benefits of Quitting. <https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco/cessation-fact-sheet>. Published December 3, 2014. Accessed October 18, 2016.

Related Information

[National Cancer Institute: Harms of Cigarette Smoking and Health Benefits of Quitting](#)

[National Cancer Institute: Where To Get Help When You Decide To Quit Smoking](#)

Smokefree.gov

Offers science-driven tools, information, and support to help smokers quit

[FDA 101: Smoking Cessation Products](#)

[Varenicline \(marketed as Chantix\) Information](#)

[Bupropion hydrochloride \(marketed as Wellbutrin, Zyban, and generics\) Information](#)

[The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)

[Think It Through: Managing the Benefits and Risks of Medicines](#)

[Advisory Committees: Critical to the FDA's Product Review Process](#)