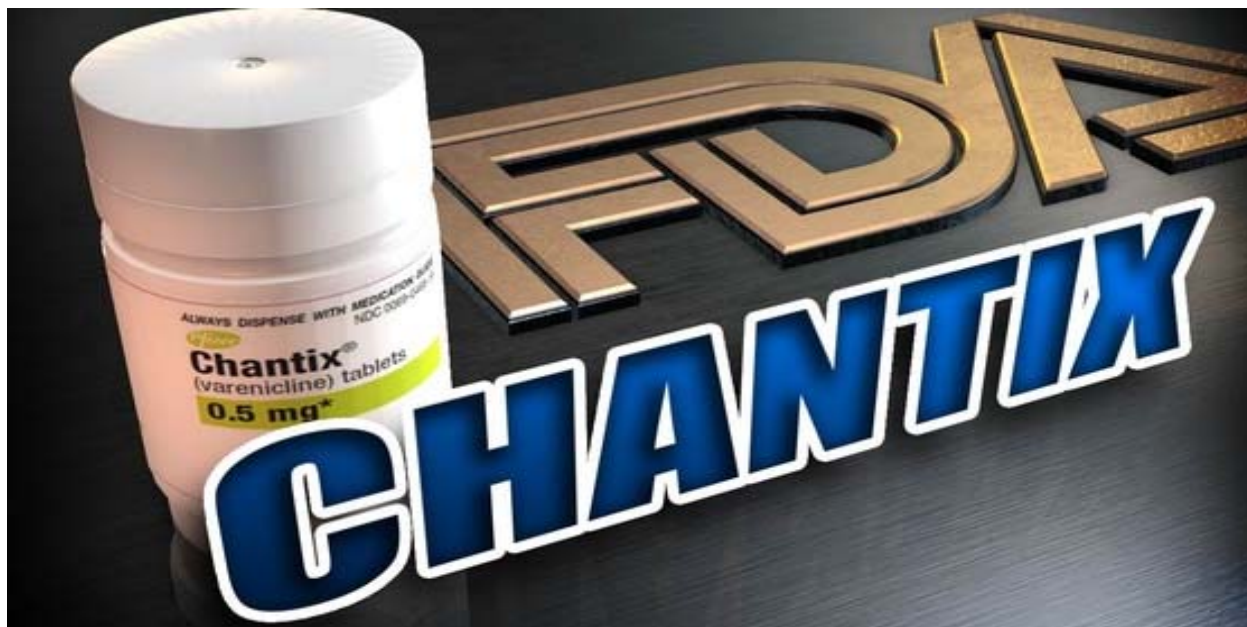


Project ECHO
Varenicline (Chantix):
The Evolving Understanding of
its Psychiatric and
Cardiovascular Effects
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Objectives

- Describe the history of FDA safety warnings of Varenicline as it relates to psychiatric and cardiovascular adverse-effects.
- Describe the current understanding of cardiovascular effects of Varenicline.
- Describe the current understanding of psychiatric effects of Varenicline.

Background

- Tobacco use (smoking in particular) is a leading risk factor for the development of cardiovascular disease (CVD).
- Smoking is independently associated with suicidal ideation, attempts and completed suicide in several large studies, after controlling for psychiatric and alcohol use disorders.

Background

(continued)

The nicotine withdrawal syndrome itself (days to months after quitting) includes:

- Depressed mood
- Anxiety
- Poor concentration
- Irritability, frustration or anger
- Restlessness
- Insomnia
- Tiredness

Timeline of Varenicline Safety Warnings

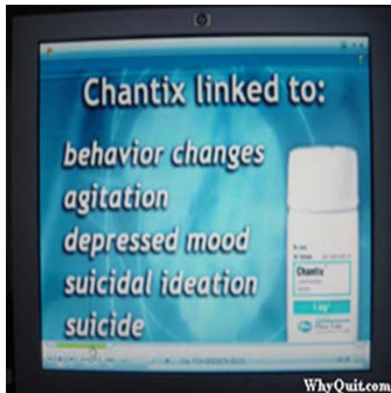
- 2006 - Varenicline approved for smoking cessation.
- 2007 - FDA starts receiving MedWatch reports of suicidal thoughts, aggressive and erratic behavior.

Timeline of Varenicline Safety Warnings

(continued)

- 2008 - FDA recommends to monitor all patients taking Varenicline for serious psychiatric symptoms.

Negative Publicity



Click to view FDA video linking Chantix to suicide



CHANTIX LAWSUIT CENTER

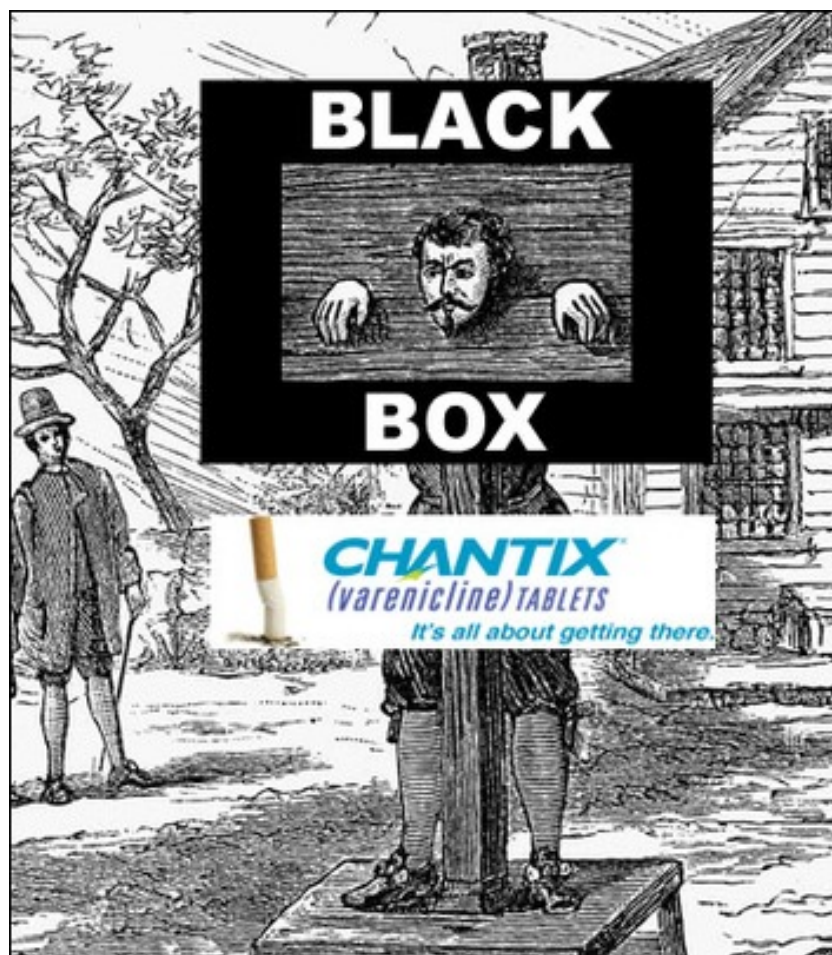
I N J U R Y L I T I G A T I O N N E W S 2 4 / 7

Have you been injured
by Chantix...

Call toll free 24 hours/day
855.688.2529

Black Box Warning 2009

- FDA requires Black Box warning on Varenicline labeling information
- FDA never recalled Varenicline
- FDA requires manufacture to conduct data re-analyses and prospective-large clinical trials to assess safety of Varenicline



WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)
- Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)
- Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)

Studies to Evaluate Neuropsychiatric Risk

- 2011 - FDA reviewed studies (DoD, VA) to evaluate risk of neuropsychiatric adverse effects associated with Varenicline
- Conclusion - No difference in risk of neuropsychiatric hospitalization between Varenicline and NRTs

Cardiovascular Risk



- 2011 - FDA Drug safety communication:
Chantix may be associated with a small, increased risk of certain cardiovascular adverse effects in patients who have cardiovascular disease.

Studies to Evaluate Cardiovascular Risk

- 2012 - FDA reviewed RCT of 700 smokers and a large meta- analysis of clinical trials
- Conclusion: Cardiovascular events are uncommon in both groups. Varenicline (0.31 %), Placebo (0.21 %).

NOT SIGNIFICANT!

Most Recent FDA Update: 2015

Alcohol Interaction:

Since 2006, 48 cases of decreased tolerance to alcohol or aggressive behavior in patients taking Varenicline and alcohol.

More than 10 million people in US have been prescribed Chantix

Most Recent FDA Update: 2015

(continued)

Seizures:

64 cases of seizures reported in patients using Varenicline. Of those 27 had history of seizures.

More than 10 million people in US have been prescribed Chantix

Most Recent FDA Update: 2015

(continued)

Neuropsychiatric adverse events:

Meta-analysis of 5 RCTs (1,907 patients: 1,130 Chantix, 777 placebo)

Result: No increase in the incidence of suicidal ideation and/or behavior, Chantix versus placebo

Most Recent FDA Update: 2015

(continued)

Neuropsychiatric adverse events:

- Pooled data analysis of 18 RCT (8521 patients: 5072 Chantix, 3449 placebo). Some had psychiatric conditions at baseline
- Result: No difference in common psychiatric events, Chantix versus placebo

Recently Published Study

Lancet Respiratory Medicine Journal (09/2015)

Chantix does not raise risks of heart attack or depression... and should be recommended to more smokers wanting to quit, scientists said.

Tracked 150,000 smokers in England for 6 months after participating in smoking cessation treatment and having been on NRTs, Bupropion or Chantix

Newest Published Study

Hot off the press: A large multinational trial (EAGLES) published LANCET April 22, 2016

Neuropsychiatric safety and efficacy of Varenicline, Bupropion, and nicotine patch in smokers with and without psychiatric disorders: double-blind, randomized, placebo-controlled clinical trial

Newest Published Study

(continued)

EAGLES Study:

1. Patients **without** a current or history of a psychiatric disorder- No difference in neuropsychiatric adverse-effects for Chantix, Bupropion, patch compared to placebo
2. Patients **with** current (stable) or history of psychiatric disorder- No difference in neuropsychiatric AEs across treatment versus placebo
3. However a 4% increase in rate of neuropsychiatric AE was observed in psychiatric cohort compared to non-psychiatric cohort across treatments and placebo

Newest Published Study

(continued)

- Limitations of EAGLES Study:
 - Study included only smokers with stable and treated psychiatric disorders. It did not include patients with substance use disorder in past 12 months
- Findings cannot be generalized to those with unstable psychiatric disorders or active substance use disorders

Newest Published Study

(continued)

EAGLES Study Conclusions:

- Smoking cessation medications (Chantix, bupropion and patch) have similar neuropsychiatric AEs to placebo among patients with or without a psychiatric diagnosis or Hx.
- Patients with psychiatric diagnosis or Hx have a 4 % increase in neuropsychiatric AEs in trying to quit smoking whether on medication or placebo.

Take Home Points

- No significance in cardiovascular or neuropsychiatric events in studies to date
- It is prudent to monitor all patients taking Chantix for serious neuropsychiatric symptoms such as changes in behavior, agitation, depressed mood, suicidal ideation and suicide behavior

Take Home Points

(continued)

- Until a patient knows how Varenicline affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink.