

Strengthen the Varenicline (CHANTIX) Boxed Warning and MedGuide

A Statement from the Institute for Safe Medication Practices (ISMP)

Abstract

ISMP believes it will cause preventable harm to patients if the prominent warnings about suicidal behavior and violence associated with varenicline (CHANTIX) are removed from the prescribing information and Medication Guide. Instead existing warnings should be clarified and strengthened.

Substantial scientific evidence shows that many varenicline psychiatric symptoms begin early in treatment, sometimes before smoking discontinuation, and worsen with continued exposure unless the drug is discontinued.

If the warnings are removed, new patients will not be alerted to watch for unexpected changes in mood, thought, and behavior. And if they seek help from medical professionals, their physicians would deny a drug relationship and urge continued treatment. The result would inevitably be life-changing tragedies of violence and suicidal behavior that could be prevented with current warnings and a timely switch to safer alternative treatments.

Varenicline is the primary suspect drug in 17,900 serious injuries from psychiatric adverse events that were reported to the FDA, 43% by health professionals. The cases describe suicidal behaviors, bizarre and reckless aggression, delusions, and homicidal and suicidal thoughts. The effects are documented in peer-reviewed studies and FDA surveillance reports that were written independently by different teams of investigators using data from different countries. More than 2,500 varenicline victims have been paid an estimated \$300 million in compensation by Pfizer for serious injuries that occurred before the Boxed Warning was required.

Currently, more than 60 drugs currently have warnings about suicidal behaviors. Varenicline should remain one of these. To remove or render ineffective this warning requires one to conclude that the results of the new Pfizer psychiatric side effects clinical trial are so definitive that these adverse effects of varenicline do not in fact exist for *any* patients. But this trial was greatly underpowered, used a novel, unvalidated measurement scale, required subjective judgements from study investigators, and detected no meaningful differences among eight treatment arms because of a defective design.

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Section 1: Lines of credible scientific evidence

Mechanism of Action

While idiosyncratic adverse effects occur, most harms from therapeutic drugs are rendered possible or probable based on the mechanism of action of the drug or its metabolites. Is it plausible that varenicline could, in some patients, cause homicidal ideation, bizarre violent acts, and suicidal behaviors?

The varenicline molecule was designed to achieve continuous but partial occupancy of $\alpha 4\beta 2$ nicotinic receptors, which in turn mediate the release of dopamine.¹ But it differs from cigarette smoking because its effects are continuous receptor occupancy while cigarette smoke results in a brief “hit.”

Varenicline interference with normal dopaminergic signaling is clinically confirmed by the most common adverse effect of varenicline, nausea and vomiting. In clinical trials it was observed in more than 1 out of 3 patients.² That this adverse effect is mediated through dopamine pathways is supported by the fact that metoclopramide and some other anti-emetic drugs block dopamine receptors, and because dopamine mediates the vomit reflex.

Evidence that interference with normal dopamine signaling can result in bizarre, extreme behaviors and loss of impulse control can be seen in the drugs for restless legs syndrome, hyperprolactinemia, and Parkinson’s disease. They are agonists of the dopamine D3 receptors and cause the loss of impulse control manifested in pathological gambling, hypersexuality, and compulsive shopping. Following our adverse event disproportionality study in *JAMA Internal Medicine*,³ the FDA recently upgraded the warnings for these drugs. While different, the behaviors are often as bizarre as those reported for varenicline.

Unpredictable effects are also to be expected from the body’s response to varenicline disruption of normal signaling rather than from direct effects from the drug itself. Since normal neurotransmission occurs in milliseconds followed by rapid reuptake or metabolism, continuous dopamine release could have at least three possible effects. 1) Amplification or behavioral triggering might occur in circuits where dopamine release was occurring, but too weak to result in depolarization. 2) Downregulation occurs when neuroreceptors are overstimulated. We can see downregulation occurring with varenicline because nausea and vomiting resolve in most cases, and the adverse effects are limited by the drug’s seven-day dose titration scheme. 3) Another possible response to signaling disruption is supersensitivity. Varenicline, by definition and design, is a partial antagonist as well as a part agonist, and in some settings might obstruct rather than enhance dopamine signaling. The response could be

production of additional neuroreceptors and future overreaction to normal signaling. In conclusion, we would expect widely varied and unpredictable effects from varenicline because dopamine receptors are found in 10 different functional areas of the brain and mediate learning, memory, rewards, attention, impulse control, decision making, sleep, and regulation of food intake.⁴ Outside the central nervous system, dopamine mediates aldosterone secretion, blood pressure, vasodilation, and gastrointestinal motility. The blackouts, blurred vision, and syncope resulting in accidents associated with varenicline⁵ are likely related to its interference with dopaminergic regulation of blood pressure and vasodilation.

Evidence from case reports

Like most new adverse drug effects, the psychiatric side effects of varenicline were initially discovered through case reports. In the months after varenicline's initial marketing, the FDA began to receive scores of adverse event reports about bizarre, violent, and suicidal thoughts and behaviors. Over time the number of case reports continued to grow. As of April 1, 2016 the FDA has received 17,872 reports of serious psychiatric adverse events, 43% from domestic or foreign medical professionals, 38% from U.S. consumers, and 19% through legal actions. When the FDA was evaluating the first wave of adverse event reports in late 2008 and 2009, its investigators were unaware they were not seeing thousands of additional adverse event reports that Pfizer had improperly submitted into the wrong electronic records system at the agency.⁶

Assessing causality

The most convincing case reports meet the established scientific criteria for evaluating a possible causal relationship. First, the patients had either no prior history of violence or psychiatric problems, or had been stable for many years. Second, abnormal thoughts, dreams and behavior began early, sometimes even after the first pills, and then got steadily worse with continued exposure and scheduled dose titration increases. Third, in many cases the abnormal thoughts, dreams and behaviors stopped on treatment discontinuation. Fourth, no plausible alternative causes were seen in the reports. There were also rechallenge cases in which symptoms stopped on discontinuation and reappeared when treatment was resumed. While this does not describe all the case reports, the most persuasive ones also shared a kind of bizarre, pointless character and loss of impulse control. This is illustrated in excerpts from our original 2014 Citizen Petition:⁷

Case # 1: Assault

By the third day of taking Chantix I was completely out of control. I woke my boyfriend up in the middle of the night and started physically beating him. I contemplated suicide about 5 times a day and contemplated homicide about 3 times a day.

This case shows early onset prior to smoking cessation, sleep disturbance, homicidal ideation, suicidal ideation, and later but not shown here, attempted suicide. Female, age 24, (ISR 5742066)

Case #2: Terrifying Nightmares

She had a nightmare on 23Dec2007 that she was lying in prison laying on a cold wet floor shackled to a corpse. On 26Dec2007 she wanted to get the key to the gun cabinet and shoot her husband." She stopped taking Chantix and "everything setting her off resolved on 28Dec2007."

This case shows a sleep disturbance so vivid it approaches a hallucination, and is followed by an apparently unrelated episode of homicidal ideation and dechallenge. Female, age 43 (ISR 5587336)

Case # 3: Anger/Aggression

She swung at her mother (who was in her late 90's) due to the extreme rage as she almost struck her and missed. She went out in the back yard and broke a weed whacker, a couple of glasses, the frame work on a couple of lamps, she threw concrete in the backyard and she began stabbing chunks of wood with the garden tools to get her rage out.

In this case report reviewed by FDA OSE the index event was suicidal ideation, but the narrative excerpt portrays uncontrolled aggression/anger and senseless violence.⁸

Case #4: Screaming and Crying

On Saturday while at home she got into a verbal argument with her mom over a minor issue and reports now that she was 'totally out of hand' and she was unable to control her impulses and was yelling and screaming and crying. She acutely became suicidal and also became homicidal threatening her mother with a shotgun. Her mother fled the house and called police. She locked herself in the bathroom and eventually calmed down.

Suicidal behavior and senseless aggressive acts occur together. Female, age 21 (ISR 5821157)

Case #5: Suicide Attempt

After 2 weeks of taking Chantix, I flew into a fit of uncontrollable rage after consuming alcohol one evening – resulting in me beating my boyfriend, followed by an attempt to take my own life. An overnight stay in the ER followed.

Senseless aggression and suicide attempt. Symptoms resolved on discontinuation. Female, age 28 (ISR 5626093)

Case #6: Homicide

Appellant was nineteen years old and had been in the service for approximately a year. Prior to enlisting, Appellant was an active member of his community and led various volunteering and mentoring projects as an Eagle Scout. Upon turning eighteen, both Appellant and his twin brother enlisted in the United States Army. After successfully completing Infantry Training and the Airborne Course, they were both selected for an appointment to the United States Military Academy Preparatory School (USMAPS), class of 2009. [Was temporarily assigned to a supply room at Fort Benning and prescribed Chantix].

Appellant had been experiencing "new and strange thoughts" including a "person [was] telling me . . . dangerous things that aren't [sic] me." These included violent thoughts of killing someone. On May 18, 2008, one month after the Army doctor prescribed Chantix, Appellant fatally attacked Private (PVT) Bulmer while he was sleeping, stabbing him to death. Prior to this attack, Appellant did not know nor had he ever interacted with PVT Bulmer.

This case includes nightmares, psychosis, homicidal ideation, senseless act, and homicide. Male, age 19. (Extracted from appeals court judgment reversing his murder conviction because the judge did not allow a CHANTIX defense of involuntary intoxication.)

Compelling cases were examined or summarized in three FDA reviews in 2008 and 2014, and in our peer-reviewed study.⁹⁻¹² All identified credible cases of a possible drug effect. The limitations of this line of evidence are that reports vary in completeness, cannot account for all potential confounders, and do not provide information about how frequently these events might occur.

Quantitative analysis of adverse events

Disproportionality analysis of adverse event reports is the third line of scientific evidence establishing that varenicline causes violence, depression, and suicidal behaviors. Three statistical methods for disproportionality analysis have been widely used: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), and a Bayesian method called the empirical Bayesian geometric mean (EBGM). One strength of disproportionality analysis is that it considers not only all reports for the study drug but also all other reports for selected comparators or the entire report population. In addition, the methods adjust for several known limitations of these data: that the reporting rates vary between drugs, and for different kinds of adverse drug events. Use of substantial time periods smooths variation in reporting over time. And unlike clinical trials it can detect adverse drug events that are both extremely rare and frequent.

Marked evidence of a relationship between varenicline and these psychiatric side effects was reported not only using all three accepted methods but in at least three different national adverse event databases: the US, the British yellow card scheme and the French regional pharmacovigilance data. The core of disproportionality analysis is calculating a difference between expected and observed adverse drug events. In a peer-reviewed study spanning five-year period, we reported that varenicline accounted for 18 times more reports of thoughts or acts of violence than expected, and more than any other approved drug (PRR = 18.0, n = 408, p < 0.01).¹³ A French team of pharmacovigilance investigators reported a ROR of 29.2 (95% CI 10.8-78.9) for varenicline and violence in that country's adverse event data, also more than any other therapeutic drug.¹⁴ The ROR method was used to compare suicidal behaviors and depression between varenicline and nicotine replacement products. The study showed an ROR of 8.4 (95% CI 6.9-10.4) for varenicline compared to nicotine replacement.¹⁵ The FDA used the Bayesian method and reported a statistically significant EBGM of 4.6 for varenicline for suicidal behavior, and 3.3 for suicidal ideation.⁹ A numerical comparison in British yellow card scheme data revealed 18 cases of assault or violence-related symptoms for varenicline, compared to 1 for nicotine replacement products with similar disproportionality for suicidal behavior endpoints.¹⁶

In conclusion, this line of scientific evidence showing that varenicline causes violent and suicidal thoughts and acts is robust. A strong association was seen using three different statistical methods, by three different, completely unrelated teams of investigators, and published in peer reviewed journals, or within internally reviewed FDA documents. The limitation of this line of evidence is while the evidence base is much larger and more comprehensive than case reports, these studies also do not provide information about how frequently these events occur.

Observational studies have also been reported, and were previously reviewed in our Citizen Petition, by the FDA staff, and by these two committees. The committees' judgement, 18-1, was that these data did not support a weakening or removal of existing warnings.

Section 2: The missing evidence not available to the committees

The scientific question of whether varenicline causes suicidal and violent thoughts and acts was also litigated for several years and at great expense in U.S. District Court. These proceedings were much more elaborate and more fairly balanced than the advisory committee meeting in 2014. In the varenicline litigation, literally millions of pages of scientific studies, data bases, email and regulatory documents were produced for examination. Both sides retained experienced experts to review the complete scientific record. The conclusions, the methods and the qualifications of experts could be and were challenged before a federal judge. The final phase in this mass tort litigation was for both sides to join in selecting bellwether cases to be tried in front of juries in open court.

On the eve of the first public trial in 2012, Pfizer agreed to compensate all the valid plaintiffs, approximately 2,500 varenicline victims, at the cost of an estimated \$300 million.¹⁷ But all of the scientific evidence and the expert reports from this lengthy proceeding were placed under seal. Pfizer required those compensated to sign confidentiality agreements. Pfizer opposed a motion to make available to these committees and others the most important confidential documents. The judge denied the motion to remove the confidentiality seals from key documents, declaring that the litigation had been concluded.

Because the details about 2,500 well-documented varenicline psychiatric cases has been suppressed, a historic opportunity has been lost to investigate the nature, duration, onset, outcome and patient characteristics of this unusual and dangerous drug effect.

Bias in previous advisory committee meeting

While the federal court proceedings provided that both sides had access to the complete scientific information and equal opportunities to present evidence, Pfizer was notably favored during the FDA advisory committee meeting in October 2014 over the same issues. Pfizer brought two rows of experts to sit near the committee, and they were given hours to present evidence. Experts who opposed Pfizer's position were limited to a few minutes each, and then Pfizer was granted still more time for rebuttal. As is the case with many FDA advisory committee meetings, meeting materials, briefing documents, and specific questions for the committee were not provided sufficiently in advance. For this new meeting, the FDA required that written testimony be submitted before the agency revealed the specific questions and the evidence that the committees would be asked to review.

In the previous meeting, the committees did an excellent job picking through this difficult situation. But the committees should remain alert that historically, advisory committee meetings are not a level playing field.

Section 3: What went wrong in the Pfizer side effects trial

It is an accepted proposition that the effects of therapeutic drugs—beneficial and harmful—are most reliably established in randomized clinical trials. They combine the statistical power of randomization with blinding and systematic observation of a medically-consistent patient population.

However, it is also axiomatic that the clinical trial must be designed and powered to detect the drug effect under study. For psychiatric effects this normally involves a sensitive and validated measurement scale (such as Hamilton Depression Rating Scale or Brief Psychiatric Rating Scale) that can be measured in every patient at every visit. Measuring adverse effects, unless prespecified, is subject to numerous limitations involving ascertainment, disaggregation, and notably, lack of statistical power.

From inception the Pfizer psychiatric side effects trial¹⁸ was a novel scientific experiment. It was unusual because the primary endpoint was safety rather than benefit. It is even more challenging to design a study of psychiatric events, which unlike QT intervals or weight gain are rare, variable and subjective. In the face of these unavoidable obstacles, Pfizer selected a composite endpoint of 12 psychiatric symptoms, combined with subjective investigator evaluation of severity—mild, moderate or severe. There was no citation or other indication in the study that this endpoint had never been used before. It was not validated, was never assessed for inter-reporter variability, and not demonstrated to be capable of assessing the events under study.

The second critical design feature was statistical power or sample size, which is based on an *a priori* assumption a hypothesized drug effect. **The study was powered to detect a moderate or severe drug event in at least 4% of the patients in any treatment group, a very large serious adverse drug effect of any kind, for any drug, in any setting.**

More problematical yet, the most prominent adverse effects under study were suicidal thoughts and behaviors, which have encountered measurement obstacles and triggered prolonged debate since Teicher reported the early fluoxetine cases in 1990.¹⁹ While more than 60 drugs now have warnings about suicidal thoughts or behaviors,¹⁵ we are not aware of any cases in which warnings have been either established or ruled out in a single randomized clinical trial. The primary reason is that the events are too rare, with event rates on the order of 1 or 2 per 1,000 to 1 per 10,000 depending on event definition. For example, the FDA evidence²⁰ supporting the warning about the increased risk of suicidal thoughts and behaviors for antiepileptic drugs required pooling 199 trials enrolling 43, 892 patients, and indicated excess event rate of 2 per 1,000. Thoughts and acts of violence are much less investigated, and the event capture through almost any standard medical criteria is even more problematical. Further evidence that expected rates for varenicline were likely occurring in a few per 1,000 could be deduced from the original safety submission for approval.²¹ The FDA identified only 1 or 2 possible events in approximately 3,800 patients, although it is likely some cases were not ascertained. A United Kingdom trial in 412 patients identified 1 typical case, but the investigators not understand it as a drug effect.²²

Given an expected event rate measured in few cases per 1,000 it was a certain recipe for failure to design a safety trial capable of detecting an effect frequency of 40 per 1,000 cases (or 4%), and relying on an unvalidated measurement scale never used as a clinical trial endpoint. This trial was underpowered by an order of magnitude.

Not only was the Pfizer side effects trial grossly underpowered, there were other problems with the aggregate endpoint. It added a subjective requirement that the event had to be moderate or severe in the judgement of an investigator. Simple inspection of the hostility endpoint element provides further evidence that event ascertainment was weak. It detected not even one case of moderate hostility in either of the placebo groups and only 2 “severe” events among all 8 trial arms and 8,100 patients. Anyone familiar with the effects of nicotine withdrawal should be skeptical of a report that

detected no moderate hostility events among 2,014 placebo patients who were unwittingly placed into cold turkey smoking cessation by the blinded trial protocol. The detection of new or worsening depression was 0.6% in the psychiatric cohort, 70% of whom had depression or bipolar disorder at baseline. Detecting so few depression events in so many patients with depression raises further questions about event ascertainment.

Finally, the Pfizer side effects trial excluded from the endpoint and event questionnaire the most frequent psychiatric adverse effect, abnormal dreams, which (as shown above) can be violent and terrifying. In the tabulation that included all spontaneously volunteered accounts of abnormal dreams or nightmares, the reported rate for varenicline was markedly lower than observed in pre-approval clinical trials. All this evidence shows that not only was the study vastly underpowered to detect suicidal and violent thoughts and acts, the events it did detect were ascertained at lower than expected rates compared to previous clinical trials.

From a statistical perspective The Pfizer side effects trial was an elaborate and expensive example of Type II error—an experiment not capable of detecting the effect under study because of a deficient design. It is no surprise that it failed to detect a statistically significant difference between 10 of the 12 treatment pairs, and even the outliers would be rendered non-significant by adjustment for multiple comparisons. Any inclusion of any of these results in the prescribing information should note prominently that it was not capable of detecting psychiatric adverse effects occurring in fewer than 4% of patients.

Section 4: What evidence is required to eliminate safety precautions?

What strength of evidence does it take to remove a Black Box warning that in place since 2009? And to do so in the face of directly conflicting evidence from different scientific methods. Neither Section 505 of the Food Drug and Cosmetic Act, nor the product labeling regulation (21 USC 201.57) address this issue directly. Nor do legal precedents or previous advisory committee cases provide substantial guidance. The committees meeting about varenicline are forced into largely unexplored legal and public policy territory with thousands of patient lives at stake.

A different impact

An advisory committee vote reject a new drug or indication has markedly different impact than a vote to eliminate or weaken an existing safety precaution. Rejecting a new drug will mean that no patients will have access to a new therapeutic option. Stripping away a Boxed Warning about the need to monitor patients for unexpected changes in mood, thought, behavior and sleep does not change the indication or availability of varenicline—which are not restricted at present. It only reduces the care with which this drug treatment is administered.

Those who have testified or monitored previous advisory committee meetings have observed occasions when FDA senior management appears and orally provides some standard intended to guide the committee, but not previously seen in law, regulation, draft guidance or briefing memo.

We urge the members of these FDA committees and the CDER leadership to have a transparent and documented discussion of what is the standard of evidence for eliminating a safety precaution in the face of credible evidence from several lines of scientific investigation.

Questions and actions

The underlying issue is one of patient safety and public health. Should physicians and patients be advised with prominent warnings to be alert to unexpected changes in mood, thought, behavior or sleep that occur during varenicline therapy. And to stop the drug immediately and seek medical evaluation should such event occur. There are three issues to consider.

1) Such warnings, it is reasonable to assume, might identify some cases in which the patient incorrectly identified varenicline as the cause of some new abnormal thought or behavior, as might occur with any label warning. But would it not be beneficial if unexpected changes in mood or behavior received immediate medical evaluation, whether ultimately proved drug related or not?

2) Suppose the existing Boxed Warning/Medication Guide cautions are eliminated or so cluttered with ambiguous language that the moral force of warning is lost? Is there a benefit to advising physicians not to monitor their patients who are discontinuing smoking with varenicline? Should patients be told to keep taking the drug even if they suspect it is causing bizarre thoughts and behaviors they have never experienced before? Or should an alternative treatment be substituted?

3.) Does the Pfizer psychiatric side effects trial provide scientific evidence so definitive and convincing that all the other lines of credible scientific evidence can be disregarded? Or is it a defective study not capable of detecting drug-related effects that occur in fewer than 4% of patients, and that was not sensitive in confirming the extent of known side effects.

In conclusion, ISMP urges the committees to recommend that for physicians, the existing Boxed Warning be retained . In addition, it should be clarified to alert the patients to report unexpected changes in mood, thoughts, behavior and sleep, and in order to substitute safer alternatives. In addition, the current Medication Guide cautions should be retained as written.

An ambiguous warning can be worse than no warning at all because not only does it render the warning ineffective, it undermines the value of all warnings and the credibility of the FDA. A clear warning does not restrict the access of any patient or physician to this treatment.

Respectfully submitted,

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