



# The Institute for Safe Medication Practices

A Nonprofit Organization Educating the Healthcare  
Community and Consumers About Safe Medication Practices

## Strong Safety Signal Seen for New Varenicline Risks

### EXECUTIVE SUMMARY

A strong signal of multiple safety problems with Chantix (varenicline), a drug to help people stop smoking, has been seen in a pilot program to identify new drug risks in adverse drug events reported to the U.S. Food and Drug Administration.

Varenicline is suspected in various adverse drug event reports of causing a wide spectrum of injuries, including serious accidents and falls, potentially lethal cardiac rhythm disturbances, severe skin reactions, acute myocardial infarction, seizures, diabetes, psychosis, aggression and suicide. The cases were analyzed and classified using computerized excerpts of adverse event reports which the FDA publishes for research use.

The FDA approved varenicline in May 2006 after granting it a priority review. Varenicline is a partial agonist of one of the nicotinic acetylcholine receptors in the brain and nervous system,<sup>1</sup> and currently the only marketed and approved drug with this mechanism of action.

In the 4<sup>th</sup> quarter of 2007 varenicline accounted for 988 serious injuries in the U.S. reported to the FDA, more than any other individual drug in this time period. By comparison the FDA received a median of 5 reports of serious injury for 769 different drugs in the 4<sup>th</sup> quarter. Only 35 drugs accounted for 100 or more reports. This large volume of reports prompted us to conduct an analysis of all adverse events for varenicline since marketing approval in 2006.

The FDA has recently issued a Public Health Advisory about one of the most marked adverse effects of varenicline, psychiatric symptoms that included “changes in behavior, agitation, suicidal ideation, attempted and completed suicide.”<sup>2</sup> However, the FDA alert provided no information about the numbers of reported neuropsychiatric events among treated smokers.

From May 2006 through December 2007, the FDA had received 227 domestic reports of suicidal acts, thoughts or behaviors, 397 cases of possible psychosis and 525 reports of hostility or aggression. These totals included 28 cases of suicide and 41 mentions of homicidal ideation, 60 cases of paranoia and 55 cases of hallucination. The categories were not mutually exclusive.

However, the adverse drug event reports for varenicline describe other kinds of serious harm for which no warnings now exist, either from the FDA or from the manufacturer, Pfizer Inc. The cases (including those with psychiatric effects) were classified using standardized medical queries developed by the pharmaceutical industry to identify potential adverse events in clinical studies and postmarket surveillance.

Adverse event reports in themselves do not establish a causal link to the drug, only that an observer suspected a relationship. Depending on the features of the specific event, it could be counted in multiple categories, and classifications are not definitive. Among the most prominent were:

- **Accidents and injuries.** A total of 173 serious events described accidental injury, including 28 road traffic accidents and 77 falls, some leading to fractures of rib, facial bones, hand, ankle, spine, and lower limbs. In these cases a variety of potential causes were identified, including loss of consciousness, mental confusion, dizziness and muscle spasms.
- **Vision disturbance.** At least 148 reports contained medical terms indicating vision disturbances, including 68 cases described as blurred vision and 26 terms indicating transient or other forms of blindness. This reported effect could also describe a mechanism that could or did contribute to accidents and injuries.
- **Heart rhythm disturbances.** The FDA received 224 domestic reports classified as potential cardiac rhythm disturbances. This category, however, was dominated by reports of sudden loss of consciousness, an event that could also have non-cardiac causes. However, this category also included smaller numbers of cardiac arrests and identifiable abnormal cardiac rhythms
- **Seizures and abnormal muscle spasms or movements.** Serious reported events included 86 cases of convulsions (seizures), 372 reports of a wide variety of movement disorders, including tremors, muscle spasms, twitching, tics, drooling, and motor hyperactivity. The extent to which these problems resolved with a reduced dose or by halting treatment could not be determined from these data.
- **Moderate and severe skin reactions.** Reported serious events included 338 cases of hives or swelling of the tongue, face, eyes, lips or other areas. In addition, 65 cases were classified as severe and included blisters, exfoliation of the skin and lips, and Stevens-Johnson Syndrome.
- **Diabetes.** The FDA has received 544 reports suggesting varenicline may be related to a loss of glycemic control. This category included many cases of weight loss or gain that could have alternative causes, but also identified numerous cases of symptoms and laboratory tests consistent with new onset diabetes.

## Recommendations

We have immediate safety concerns about the use of varenicline among persons operating aircraft, trains, buses and other vehicles, or in other settings where a lapse in alertness or motor control could lead to massive, serious injury. Other examples include persons operating nuclear power reactors, high-rise construction cranes or life-sustaining medical devices. Based on reports of sudden loss of consciousness, seizures, muscle spasms, vision disturbances, hallucinations, paranoia and psychosis, we believe varenicline may not be safe to use in these settings. The extent to which varenicline has already contributed to accidental death and injury has not yet been investigated because these adverse effects had not been previously reported. The Federal Aviation Administration approved varenicline for use by airline pilots<sup>3</sup> before most of these reports were available.

In addition, we recommend that patients and doctors exercise caution in the use of varenicline and consider the use of alternative approaches to smoking cessation.

Finally, we urge the FDA and the manufacturer to provide warnings to doctors and patients for those adverse effects that can be adequately documented through existing data, and to undertake on a priority basis epidemiological studies or other research to assess other potential risks. We promptly notified the FDA of our findings.

This report was written by:

Thomas J. Moore, Senior Scientist, Drug Safety and Policy, ISMP

Michael R. Cohen RPh, MS, ScD, President, ISMP

Curt D. Furberg, MD, PhD, Professor of Public Health Sciences, Wake Forest University School of Medicine.

Institute for Safe Medication Practices  
200 Lakeside Drive, Suite 200  
Horsham, PA 19044  
215-947-7797  
[www.ismp.org](http://www.ismp.org)

Corresponding Author  
Thomas J. Moore  
[tmoore@ismp.org](mailto:tmoore@ismp.org)

## Full Report

### BACKGROUND

Varenicline was approved as an aid to smoking cessation treatment, joining nicotine replacement products and the antidepressant drug bupropion, marketed as Zyban, for this medical use. Varenicline, however, was reported to achieve its effect through a novel mechanism of action, through partially blocking and partially stimulating a type of nicotinic acetylcholine receptor. It was derived from cytisine, an antismoking drug used in Europe for many years.<sup>4, 5</sup> Acetylcholine receptors play numerous roles in the brain and body and are central to muscle contractions—both voluntary movement and the heart muscle contractions as well as the tone of the smooth muscles that line the blood vessels.

Pfizer research scientists who developed the drug focused on a particular role played by one of the subtypes of receptor, the  $\alpha_4\beta_2$ . Varenicline was most active against this subtype and specifically these receptors increase the release of dopamine in the brain.<sup>5</sup> Dopamine, in turn, plays a major role in addiction, mood, and muscle movement. Many antipsychotic drugs block dopamine receptors, but they also cause movement disorders. The loss of muscle control seen in Parkinson's disease is the result of the destruction of dopamine-producing cells in the brain. Pfizer scientists theorized that the mixture of blocking and stimulating nicotinic acetylcholine receptors would replace some of the pleasure of smoking through stimulating dopamine release, and block or reduce the effects of nicotine when present.

In clinical studies, varenicline produced 52-week quit rates of approximately 22 percent.<sup>6-9</sup> Similar quit rates have been observed in nicotine gum,<sup>10, 11</sup> although Pfizer has claimed an advantage over the nicotine patch in a comparative study it conducted.<sup>6</sup> However, the varenicline results may not be achieved in clinical practice because the initial 12-week treatment program included weekly clinic visits with counseling. More importantly, both the benefits and the safety profile of varenicline were likely influenced by the type and number of patients excluded from the Phase 3 trials. For example, the longest varenicline safety and efficacy trial excluded patients with the following:<sup>12</sup>

- Recently treated for depression, bipolar disorder, psychosis or panic disorder.
- Experienced clinically significant allergic reactions to any drug.
- Had any abnormal laboratory findings.
- Cardiovascular disease within six months
- Were using over-the-counter or prescribed stimulants or diet pills
- Had a history of drug or alcohol abuse or dependence

The trials also prohibited concomitant use of other psychologically active drugs, including stimulants, antidepressants, tranquilizers, antipsychotics, mood stabilizers, naltrexone and anticonvulsants.

Varenicline was approved first in the United States in May of 2006, and then later in the year in Europe. The manufacturer reported that 5 million persons worldwide had taken varenicline; we estimate this includes approximately 3.5 million persons in the United States.<sup>13</sup>

### **Why this study was conducted**

The signal for varenicline was observed in an Institute for Safe Medication Practices (ISMP) pilot program to identify emerging drug risks and new medication errors through monitoring FDA adverse event reports on a quarterly basis. The agency publishes computer excerpts of adverse events from which all identifiable personal information has been removed. The report narrative is replaced by a series of medical terms that describe the event that has occurred.

Adverse event reporting is voluntary for consumers and health professionals. However, manufacturers are required to investigate and report all adverse events of which they happen to learn. The reporting rate is unknown, variable and poorly studied. Crude published estimates suggest that from 1% to 10% of serious adverse events are reported.<sup>14</sup> We maintain a copy of all adverse events reported to the FDA--which is thought to be one of the largest drug safety databases in the world.

Two analytical approaches have traditionally dominated the use of these adverse event data. One technique, called a case series, is to analyze a group of carefully selected, uncomplicated reports. The FDA itself analyzes its adverse event data on a case-by-case basis. A second approach, called data mining, searches for signals through unexpected connections between drugs and event characteristics.

The signal for varenicline, however, was identified using a third approach, which was to monitor the flow of quarterly reports in order to detect changes in the numbers of serious events and other trends.

Varenicline crossed a first signal threshold in the 4<sup>th</sup> quarter of 2006 when it appeared for the first time among a small group of drugs that accounted for 100 or more reports of serious injury in a calendar quarter. By the 2d quarter of 2007 it ranked 3d among all drugs in the United States.

By the 3rd quarter of 2007 varenicline produced a signal not previously seen for any other drug. It produced more serious reports than any other drug for multiple types of events: more potential cases of angioedema, cardiac arrhythmia, diabetes and severe cutaneous injury. By the 4<sup>th</sup> quarter of 2007 varenicline accounted for more reports of serious drug adverse events in the United States than any other drug. (Table 1)

| <b>Table1. Leading Suspect Drugs 2007/Q4*</b> |              |
|-----------------------------------------------|--------------|
| <b>Drug</b>                                   | <b>Cases</b> |
| Varenicline                                   | 988          |
| Interferon Beta                               | 640          |
| Etanercept                                    | 555          |
| Infliximab                                    | 554          |
| Fentanyl                                      | 404          |
| Oxycodone                                     | 372          |

\*Principal suspect drug/US only/serious

The cases selected for this analysis are shown in Table 2 and consist of all U.S. reports of serious injury since the drug was approved. These are the same criteria used in the quarterly monitoring program except that whenever updated or revised reports were found, the latest version was used. These criteria omit two important groups of reports that could contribute substantially to understanding the safety profile of the drug. We excluded 1608 foreign reports because monitoring focuses on risks to patients in the United States. We excluded 473 direct reports to the FDA which had ambiguous coding for the severity of the reaction. “Other serious” could not be distinguished in these data from “other than serious.”

| <b>Table 2. Case Selection</b> |        |       |
|--------------------------------|--------|-------|
|                                | Number | Pct   |
| All Reports                    | 6363   | 100%  |
| Exclusions*                    |        |       |
| Prior reports                  | 1509   | 23.7% |
| Foreign                        | 1608   | 25.3% |
| Not serious                    | 473    | 7.4%  |
| Not principal suspect          | 415    | 6.5%  |
|                                |        |       |
| Cases selected                 | 3063   | 48.1% |

\*Report could be excluded for more than 1 reason

## RESULTS

Table 3 describes the 3063 reports included in this analysis. The FDA defines a serious adverse event as one that results in death, disability, a birth defect, hospitalization (initial or prolonged), is life threatening or requires intervention to prevent harm. The agency also allows an “other serious” category that might include events such as skin cancer or cardiac rhythm disturbances that did not result in hospitalization.

The patients characteristics show those experiencing serious injury were predominantly female (69%) and median age was 50. Compared to our previously published assessment of all reports to the agency over an 8-year period,<sup>14</sup> the varenicline reports have a greater share of reports from females (69% vs 55%), from consumers (57.3% vs 25.9%), and a substantially lower proportion of reported deaths (2.5% vs 17%). Varenicline also had a smaller proportion of reports submitted directly to the FDA (8% vs 19%) probably because of problems with the classification of “other serious” adverse events.

| <b>Table 3. Reports Overview</b> |               |            |
|----------------------------------|---------------|------------|
| <b>n = 3063</b>                  |               |            |
| <b>Report Type</b>               | <b>Number</b> | <b>Pct</b> |
| Direct to FDA                    | 246           | 8.0%       |
| Mfr-Expedited                    | 2817          | 92.0%      |
| Mfr-Periodic                     | 0             | 0.0%       |
|                                  |               |            |
| <b>Report Source</b>             |               |            |
| Consumer                         | 1755          | 57.3%      |
| Health Professional              | 1045          | 34.1%      |
| Lawyer                           | 2             | 0.1%       |
| None Stated                      | 261           | 8.5%       |
|                                  |               |            |
| <b>Outcome Group</b>             |               |            |
| Death                            | 78            | 2.5%       |
| Disability                       | 64            | 2.1%       |
| Serious                          | 2921          | 95.4%      |
|                                  |               |            |
| <b>Patient Population</b>        |               |            |
| Median age                       | 50            |            |
| Percent female                   | 69%           |            |

To evaluate types of reactions we used Standardized Medical Queries (SMQ) developed by the pharmaceutical industry to identify types of adverse reactions in clinical trials and postmarketing adverse event reports.<sup>15</sup> The SMQs were developed with explicit medical criteria and subject to validation testing. However, these selection criteria do not provide definitive assessments but rather are intended to identify potential cases for additional review. To identify vision disturbances, we used a similar but slightly different kind of category called a High Level Group Term (HLGT) which is used to group similar medical terms in various body systems.<sup>16</sup>

In Table 4 we provide event counts for selected SMQs that were chosen for biological plausibility, association with other drug therapy, appropriately specific criteria, and substantial numbers of cases. Because the individual SMQs varied in specificity and

suitability we evaluate the strengths and weaknesses of individual SMQs shown in the discussion section.

| <b>Table 4. Selected Adverse Event Types*</b> | <b>Cases</b> |
|-----------------------------------------------|--------------|
| Accidents and injuries                        | 173          |
| Angioedema                                    | 338          |
| Cardiac arrhythmias                           | 224          |
| Convulsions                                   | 86           |
| Embolic and thrombotic events                 | 139          |
| Extrapyramidal syndrome                       | 372          |
| Hyperglycemia/new onset diabetes mellitus     | 544          |
| Hostility/aggression                          | 525          |
| Psychosis and psychotic disorders             | 397          |
| Suicide/self-injury                           | 227          |
| Severe cutaneous adverse reactions            | 65           |
| Vision disturbance**                          | 148          |

\*Events frequently occur in multiple SMQs

\*\* Event type selected by High Level Group Term

## Other medications

While varenicline was the principal suspect drug in every case included in this report, the patients frequently were taking other medication. Among the serious injury cases, patients were taking a median of 2 other medications that included prescription drugs, over-the-counter drugs, vitamins, herbal products, calcium supplements and alcohol. However, one-third of all cases involved no other reported medication; another 14% listed only one other medication. At the other extreme, in 10% of the reported cases the patients reported taking nine or more medications. A total of 126 cases included a report term indicating a suspected drug interaction.

The top 10 most frequently listed other medications are shown in Table 5 and are widely used over-the-counter and prescription medications in this patient population. However, numerous other cases did include co-administration of psychoactive drugs including antidepressants, antipsychotic drugs and opioid analgesics.

| <b>Table 5. Other medication taken</b> |              |
|----------------------------------------|--------------|
| <b>n = 3063</b>                        |              |
| <b>Compound</b>                        | <b>Cases</b> |
| Multivitamins                          | 250          |
| Acetylsalicylic acid                   | 248          |
| Alprazolam                             | 216          |
| Atorvastatin                           | 184          |
| Levothyroxine                          | 180          |
| Albuterol                              | 175          |
| Fluticasone; salmetrol                 | 161          |
| Estrogens                              | 159          |
| Metoprolol                             | 146          |
| Clonazepam                             | 145          |

An additional perspective on the adverse event profile of varenicline may be seen in Table 6—a ranking of the most frequent specific medical terms extracted from all reports. It serves as a crosscheck of the adverse event reports because these terms can be compared with clinical trial results and the product labeling. Note that each report contains one or more terms. (For example a report might cite nausea and abnormal dreams or headache and weight increased.)

| <b>Table 6. Frequent Medical Terms</b> |     |
|----------------------------------------|-----|
| <b>n = 3063</b>                        |     |
| Nausea                                 | 593 |
| Depression                             | 287 |
| Insomnia                               | 242 |
| Abnormal Dreams                        | 238 |
| Feeling Abnormal                       | 223 |
| Vomiting                               | 221 |
| Anxiety                                | 217 |
| Dizziness                              | 216 |
| Headache                               | 215 |
| Fatigue                                | 184 |
| Suicidal Ideation                      | 159 |
| Dyspnea                                | 158 |
| Malaise                                | 157 |
| Weight Increased                       | 141 |
| Weight Decreased                       | 136 |

## Deaths

In the United States 78 deaths were reported in which varenicline was the principal suspect drug. While many reports contained limited detail, there were 28 reports of suicide, and numerous reports suggesting cardiac causes, both thromboembolic and arrhythmic. Compared to the overall sample, deaths were more likely to be men (59% vs 33%) and to have been reported by medical professionals (49% vs 34%).

## DISCUSSION

These data provide a strong signal that the risks of varenicline treatment have been underestimated, and show that a wide spectrum of serious injuries are being reported in large numbers. In addition to the data analyzed for this report are 1608 foreign reports that are consistent with the results reported here. Drug regulatory authorities in Canada and Europe have also issued alerts about possible psychiatric effects.<sup>17 18</sup>

Table 1 shows that in the 4<sup>th</sup> quarter of 2007, the other highest ranked drugs (e.g. fentanyl, interferon beta, etanercept) are all high alert drugs (most with black box warnings), are intended for serious illness in patients and have benefits that are accompanied by substantial risks. In comparison, varenicline is intended for use in healthy people to help stop smoking.

In addition, most of these potential adverse events are biologically plausible effects of a novel drug altering the function of a neuroreceptor performing many important functions throughout the body.

While it is likely that some individual reports will describe complex events for which there are alternative causes or contain other information to render a relationship to the drug less likely, the sheer number of reports is large for most event types listed.

However, the SMQs provided varied levels of confidence in ascertaining specific types of adverse events. Some SMQs (notably accidents, angioedema, convulsions, severe cutaneous injury) are relatively clear description of specific adverse events frequently linked to drug therapy. While scrutiny of each individual case might uncover alternative mechanisms of causation, it seems unlikely that all or even most could be discounted.

The two cardiac SMQs (cardiac arrhythmias and embolic/thromboembolic events) raise special problems of interpretation. In the case of the cardiac arrhythmias, many of the cases were thus classified because of reports of syncope and loss of consciousness. These events could be occurring through other mechanisms. In the case of embolic/thromboembolic events the challenging issue is alternative causation. While the cases included numerous reports of heart attack, stroke or pulmonary embolism, a population of smokers trying to quit can be expected to have numerous risk factors for such events. Establishing a link to these serious but common medical disorders is problematical without data from controlled clinical trials. We note, however, the FDA

voiced similar uncertainty in its safety review of varenicline: “The serious adverse event data suggest that varenicline may, possibly increase the risk of cardiac events, both ischemic and arrhythmic, particularly over longer treatment periods. This finding is far from definitive.”<sup>19</sup>

The diabetes SMQ raised different issues of interpretation. While 544 cases is a large number, this category was dominated by many cases of weight gain and weight loss. Weight gain in particular would be expected in a population giving up smoking. Even disregarding these cases, the category included numerous cases involving elevated blood glucose, hunger, thirst, frequent urination—all classic indications of new onset diabetes mellitus.

An additional question is the extent to which the large volume of reports, notably the neuropsychiatric events, might be explained by preexisting illness or other psychiatric drugs that were also being taken. However, these data show that no other drug was listed in one-third of all serious events, and numerous other medications—such as multivitamins, cholesterol lowering drugs, calcium supplements and estrogens—would be unlikely suspects. However, since the clinical trials of varenicline prohibited taking an overwhelming majority of drugs active in the nervous system, we cannot exclude the possibility of a potent interaction with one or more other drugs, especially psychiatric drugs.

### **Strengths and limitations of these data**

The data used for this report have several strengths. Because of the large numbers of patients exposed to the drug, these data are capable of detecting events that might not show clearly in relatively small, relatively short clinical trials. A large share of these reports were investigated and submitted by the drug manufacturer, presumably with consistent procedures, and potential events were selected using criteria that had been previously undergone validation testing. In addition, these events occurred under real world conditions and not the narrowly selected patient population in the clinical trials.

Nevertheless, these data have sufficient limitations that we describe these overall findings as a signal that requires further investigation and confirmation. Among the most important limitations are that these reports do not establish causality; most patients were taking multiple drugs; the event classification tool is limited to identifying potential cases and is not definitive. Reporting is voluntary for consumers and health professionals and little is known about reporting rates. Crude published estimates show that from 1% to 10% of all serious events are reported, but with wide variation among drugs, event times and over time.

An additional possibility to consider is whether the varenicline report totals were artificially increased by some factor not apparent in the reports themselves. For example, large numbers of reports for thalidomide are submitted because a controlled access program for all patients causes the manufacturer to learn about and report all serious events that occur.

Adverse event reporting rates can also be increased by media publicity about FDA warnings or other actions that publicize a drug adverse effect. On November 20, 2007 the FDA published an “Early Communication” about reports of “suicidal thoughts, aggressive acts and erratic behavior.”<sup>20</sup> Then, on February 1, 2008, the agency issued a more formal warning, a Public Health Advisory.<sup>2</sup>

We judged it unlikely that publicity from the FDA’s initial “Early Communication” in late November a significant effect on the reporting rate. There is a substantial lag that involves the time for public awareness to develop about a newly reported drug risk, for a manufacturer to receive the information and write an initial report, its transmission to the FDA and appearance in the FDA system. In addition, it seemed unlikely that publicity about neuropsychiatric adverse events could account for reports of other serious but unrelated adverse events. However, it would not be surprising to discover that publicity over the FDA’s February 2008 health advisory contributed to increased reports in the first quarter of 2008.

It is likely that Pfizer’s direct to consumer marketing program could have generated additional reports. The Chantix web site offers email and telephone coaching. Through this mechanism, the company could learn of serious adverse events which it would be required to report. On the other hand, these reports should be of high quality, since the company would anticipate that this effect would occur. All these effects tend to drive the voluntary reporting rate closer to the true incidence.

## **Conclusions**

We emphasize the recommendations outlined in the executive summary. We have concern about the use of varenicline by persons in settings where the risk of accident is high; we recommend doctors and patients exercise caution in the use of varenicline and consider alternative methods of smoking cessation. The FDA and the manufacturer should on a priority basis assess the information available and conduct additional research where current data are insufficient to resolve questions about the safety of varenicline.

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