A Case Study of Serious Adverse Event Reporting: Chantix

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Abstract

The smoking cessation drug Chantix (varenicline) is associated with many serious neuropsychiatric adverse events (AE's). The FDA has attempted to minimize these events to improve consumer protection. This research assessed how effective these FDA actions (the new format for the Prescribing Information under the Physician Labeling Rule (PLR), the addition of the boxed warning, and the REMS) were in reducing the number of serious neuropsychiatric AE's associated with Chantix. A list of sixteen serious AE's was compiled from the serious adverse event reports obtained from the FDA's Adverse Event Reporting System (FAERS). The total(s) of the serious AE's were then viewed over time in relation to the three significant FDA actions. The FDA actions had no apparent effect on the number of serious neuropsychiatric AE's associated with Chantix.

Introduction

Chantix (varenicline) is a smoking cessation medication market by Pfizer and approved by the FDA on May 10, 2006. This medication if used in combination with behavior modification and counseling can assist patients to quit smoking. It is a nicotinic receptor partial agonist that works by attaching itself to nicotine receptors so that nicotine does not. Through this mechanism dopamine is released, however in lesser amounts then what would be produced with nicotine. ("Chantix," 2015) Chantix is one of only two non-nicotine approved products for smoking cessation. The other product is Zyban (bupropion). The difference between the two products is that Chantix interferes with brain receptors that respond to nicotine thereby reducing the amount of physical and mental pleasure one receive from smoking and also weakens the symptoms that come with nicotine withdrawal. While Zyban, is an antidepressant that works by acting on brain chemicals associated with cravings for nicotine. (Thompson, 2011)

Like most drugs, Chantix is associated with many adverse events. Some serious adverse events reported during the post-marketing period were neuropsychiatric symptoms and suicidality, seizures, accidental injury, cardiovascular events, angioedema and hypersensitivity reactions, and serious skin reactions (Ogbru, n.d). When such serious adverse events become reoccurring and have a significant impact on the users of the drug, the FDA may intervene by requiring the sponsor to make changes to the prescribing information of the drug and implement strategies to evaluate and mitigate the risks.

Purpose

The purpose of this study is to determine if the number of serious neuropsychiatric AE reports associated with Chantix decreased after the implementation of the following events:

- The addition of the boxed warning
- The implementation of the Risk Evaluation and Mitigation Strategy (REMS)
- The new format for the Prescribing Information (PI) under the Physician Labeling Rule (PLR)

Background

FAERS. The data in this study is obtained from the FDA's Adverse Event Reporting System (FAERS). This computerized database contains information on adverse events and medication errors submitted to the FDA. It is designed to support the FDA's post marketing safety surveillance program for approved drugs and biologics. The reports in the database are voluntarily submitted by healthcare professionals and consumers. If manufacturers receive reports from healthcare professionals or consumers, then they are required to send those reports to the FDA to be entered into FAERS. ("FDA," n.d)

The reports submitted to this system are evaluated by clinical reviewers from the Center for Drug Evaluation (CDER) and the Center for Biologics Evaluation and Research (CBER). If potential safety concerns arise, further evaluations using larger databases may be conducted. And based on these evaluations, the FDA may take regulatory actions such as updating the drug's labeling information, placing restrictions on the use of the drug, communicating the new safety information to the public or removing the product from the market, a rare event. ("FDA," n.d)

“Physician Labeling Rule” (PLR). The “Physician Labeling Rule” (PLR) is the term used to refer to the regulation that became effective on June 30, 2006. This rule revises the regulations to require that the labeling contain highlights of prescribing information section, a table of contents as well as a full prescribing information section. It also reorders certain sections of the labeling requiring minor content changes as well as some graphical requirements. The prescription drug labeling information, also known as prescribing information (PI), ‘‘professional labeling,’’ ‘‘package insert,’’ or ‘‘direction circular,” contains the essential information to use the product in a safe and effective manner. (“FDA,” 2006) According to the FDA, the term “labeling” is defined as all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article. (21 U.S.C. 321(m)) The labeling is written for physicians to provide information so that they may make accurate prescribing decisions. (“FDA,” 2006)

Boxed Warning. The boxed warning is considered to be the FDA’s strongest warning. It is used to highlight certain information to the prescribing physician about the drug. According to the FDA it can be used in three situations, when there is an adverse event which is so serious in proportion to the potential benefit from the drug (i.e. a fatal, life-threatening or permanently disabling adverse reaction) and should be considered in assessing the risk and benefit of using the drug. Or in a situation in which the serious adverse event can be prevented or reduced in frequency or severity by the appropriate use of the drug though patient selection, careful monitoring and avoiding the drug’s use in specific clinical situations. The third situation is when the FDA approves a drug with

certain restrictions to ensure that it is safely used as FDA concluded that the drug can be safely used only if its distribution and use were restricted. ("FDA," 2011)

Risk Evaluation and Mitigation Strategy (REMS). The Risk Evaluation and Mitigation Strategy (REMS) is a required risk management plan which uses risk minimization strategies beyond the professional labeling to ensure that the benefit of a drug outweighs its risk. The FDA can require a REMS before approval of a drug if it determines that a REMS is necessary to ensure that the benefits outweigh the risks. It can also require a REMS after the approval of a drug if it becomes aware of new safety information in which a REMS might be necessary to ensure that benefits outweigh the risks. The risk must be a serious risk and must be documented in the drug's labeling information. The REMS can include any of the following: a Medication Guide or Patient Package Insert, Communication Plan, Element to Assure Safe Use (ETASU) and an Implementation System. ("FDA," n.d)

Chantix. This drug went through a PI format switch, a boxed warning labeling revision and the requirement of a REMS. A boxed warning was required to be added to the PI on July 2009, which included warnings on neuropsychiatric symptoms associated with the drug's use. These warning included changes in behavior, hostility, agitation, depressed mood, and suicide related events, including ideation, behavior, and attempted suicide (See Appendix A). Healthcare professionals were advised to monitor their patients for such symptoms. Consumers were also advised to be aware of such symptoms and were recommended that they stop taking Chantix and to contact their physicians if they experienced such symptoms. ("FDA," 2009) In addition, as the FDA became more aware of neuropsychiatric symptoms (change in behavior, depression, suicide thoughts or

actions) during post-marketing experience of Chantix, it therefore required a REMS in the form of a medication guide which was effective as of October, 2009 (See Appendix B). (“FDA,” 2013) Lastly, the labeling information for Chantix was changed to the new format required under the PLR in April, 2010.

Literature Review

The Institute for Safe Medicine Practices (ISMP) is the nation's only nonprofit organization that is entirely devoted to medication error prevention and safe medication use. It is known as a premier resource for impartial, timely, and accurate medication safety information. ('ISMP," n.d) This organization generates reports quarterly which monitor the FDA's MedWatch reports as well as the FAERS database. The ISMP has been monitoring Chantix since 2008. Their analyses are based on FDA's quarterly reports on the FDA Adverse Event Report System or FAERS. The monitoring reports have focused on things such as which drugs were responsible for the most serious adverse event cases reported, what kind of serious adverse events are reported with certain drugs (cardiovascular events, psychiatric events etc.) as well as other analyses. With regards to Chantix, they carried out several analyses in which they compared Chantix to other drugs. Their reports generated significant findings.

In May, 2008 the ISMP conducted an analysis of all serious adverse events for Chantix since marketing approval in 2006 though monitoring the FDA's quarterly reports. They found that by the 4th quarter of 2007 Chantix accounted for more reports of serious drug adverse events in the United States than any other drug. According to the ISMP the FDA received 227 domestic reports of suicidal acts, thoughts or behavior, 397 cases of possible psychosis and 525 reports of hostility or aggression. ("ISMP," 2008) These findings in addition to the additional findings presented in Table 1.

Furthermore, in the ISMP's report on the third quarter of 2008 it was found that Chantix "continued to account for more reports of serious psychiatric side effects than any other prescription drug". It also found that since the drug's approval, 30 possible

cases reporting physical assault, 148 cases involving homicidal thoughts and 331 cases of aggression (see Table 1)**.** (“ISMP,” 2009) For the fourth quarter of 2008, the ISMP reported that the total serious events for Chantix were about half of those reported for the fourth quarter of 2007. And that the drug’s sales for the fourth quarter of 2008 were also about half of those made in the fourth quarter of 2007. (“ISMP,” 2009)

For the second quarter of 2010, Chantix was found to have the most reports in three different psychiatric adverse events than any other monitored prescription drug. These side effects were clinical depression with 130 reports, hostility/aggression with 112 reports and psychosis with 70 reports (see Table 1). The report also found that there was an improvement in the suicidal and self-injurious behavior category. For this category, Chantix had the fewest reports and it did not outnumber all of the other monitored drugs. (“ISMP,” 2011) Lastly, in September 2014, the ISMP released a report in which it found that Chantix was the number one leading suspect drug in three psychiatric adverse events, thoughts of suicide, self-injury, and homicide in data obtained from 2007 until the third quarter of 2013. (“ISMP,” 2014)

Table 1: Summary of the ISMP's findings in 2007, 2008, and 2010

Quarter	**AE**	**Number of Reports**
4th Quarter-2007	Suicidal acts, thoughts or behavior	227
	Psychosis	397
	Hostility or Aggression	525
	Suicide	28
	Homicide Ideation	41
	Paranoia	60
	Hallucination	55
3rd Quarter-2008	Physical Assault	30
	Homicidal Thoughts	148
	Aggression	331
2nd Quarter-2010	Clinical Depression	130
	Hostility/Aggression	112
	Psychosis	70

Methods

The research question was addressed through an analysis of the number of serious neuropsychiatric adverse events of Chantix. The adverse event reports for Chantix were obtained from the FDA through a Freedom of Information (FOI) request. The FOI request was made on March 7, 2015, requesting records for "neuropsychiatric and suicidal Adverse Events of the drug Chantix (varenicline). Specifically adverse events that include: self-injury/self-harm and self-injury/self-harm ideation, homicidal ideation, suicidal ideation, suicide attempt, and completed suicide". The time range that was specified in the request was from the time the drug was approved (May 10, 2006) until December 31, 2014. The FDA mailed these records on a CD-ROM on March 25, 2015. The CD-ROM contained reports of all adverse events associated with Chantix that were entered in the FAERS database from August 14, 2006 until March 19, 2015. But only data through December 2014 were analyzed for this research.

For this research, a list of sixteen serious adverse events was selected for tabulation from August 14, 2006 until December, 31, 2014. The sixteen specific serious adverse events were depression, aggression, hostility, anxiety, panic, hallucination, paranoia, delusion, mania, self-injurious ideation and behavior, homicide ideation, suicide ideation, suicide attempt, and completed suicide. The adverse events were plotted by monthly incidence for the time period analyzed. The months for the labeling changes and the REMS were superimposed on the same graph. For this specific graph each AE in each report was counted. For an example, if a report contained depression, anxiety and suicide attempt, each of these AE's was counted as one point in its own separate category or line

graph. Thus, this graph contains sixteen separate line graphs, each corresponding to a specific serious AE.

A second graph was plotted with the sum of all of the sixteen serious AE's. Months of the labeling changes and the REMS were also superimposed on this graph. For this graph, each report that contained any of the sixteen AE's was counted as one point on this graph. Even if a report contained three of the sixteen AE's, it counted as a single point. In other words, this graph represented the number of reports or cases that contained any of the sixteen serious AE's. Consequently, this graph contains only one line graph.

Results

Of the 57,794 reports analyzed in this study, 14,084 of these reports contained one or more of the sixteen serious neuropsychiatric adverse included in this study, which is approximately 24% of all the serious adverse event reports submitted to the FDA regarding Chantix from 2006 through 2014. This information is presented in Table 2. On the other hand, Table 3 represents the total number of occurrences for each separate adverse event.

Figure 1 contains a single line graph that represents the sum of all of the sixteen serious adverse events recorded from 2006 through 2014. Figure 2 contains sixteen line graphs; each line is a different color and represents a single serious adverse event (i.e. depression, anxiety etc.). This figure represents the information presented in Table 3. The three black vertical lines all correspond to the most significant actions that the FDA mandated which are the addition of the boxed warning (July, 2009), implementation of the Risk Evaluation and Mitigation Strategy or REMS (October 2009) and the PI's switch to the new labeling format (April, 2010).

Table 2: Total number of reports that contain neuropsychiatric AE's from August 2006 through 2014

Number of reports with a neuropsychiatric AE	14,084
Total number of reports in database	57,794

Table 3: Total number of each serious AE from 2006 through 2014

AE	**Total Number**
Depression	7793
Aggression	2331
Hostility	344
Anxiety	4621
Panic	853
Hallucination	1075
Paranoia	699
Delusion	185
Mania	295
Psychosis	470
Self-Injury	248
Homicide Ideation	451
Suicide Ideation	3369
Suicide Attempt	1892
Suicide Behavior	276
Completed Suicide	608

Figure 1: Total of all serious neuropsychiatric AE's per month from 2006 through 2014

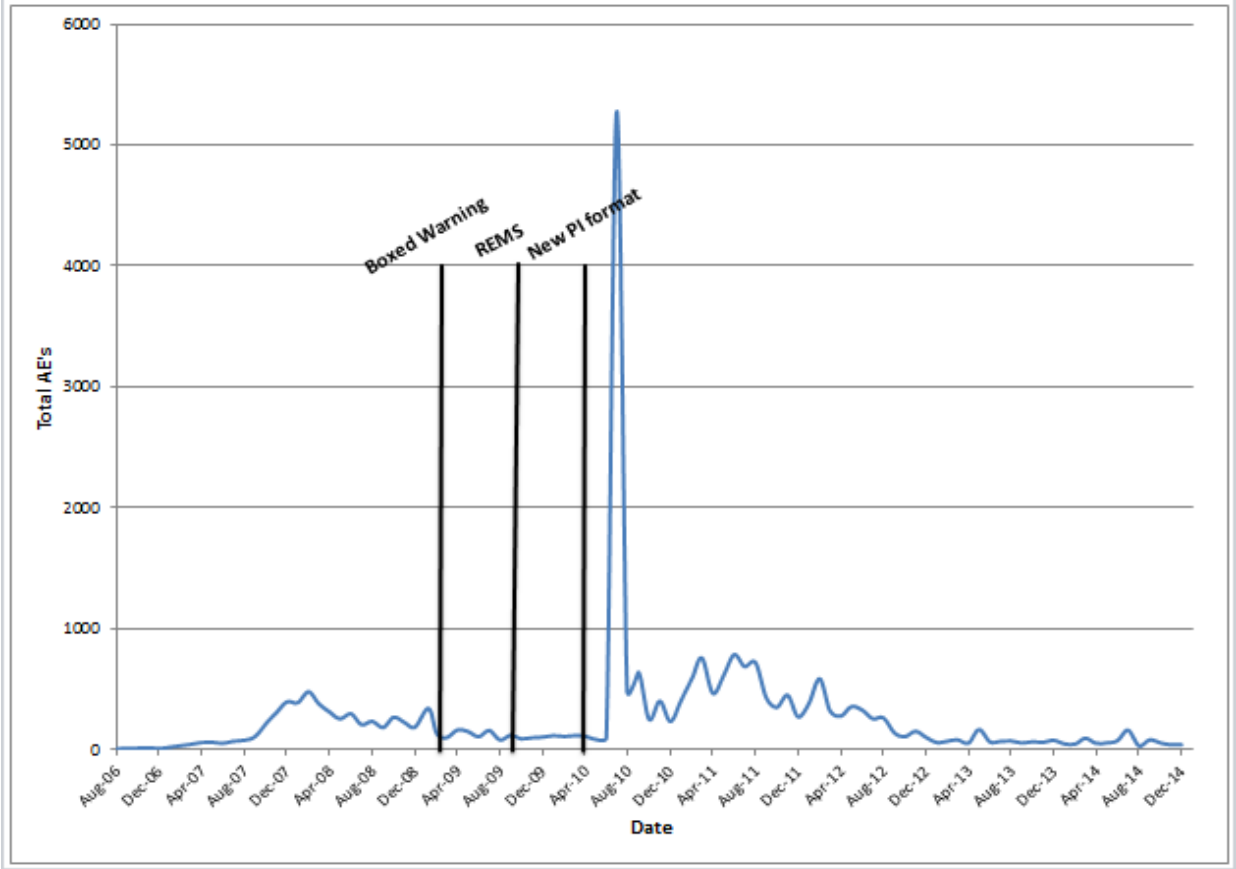

Figure 1: Total of all adverse events of all of the sixteen serious neuropsychiatric adverse events over time from August 2006 through December 2014.

Figure 2: Number of serious neuropsychiatric AE's per month from 2006 through 2014

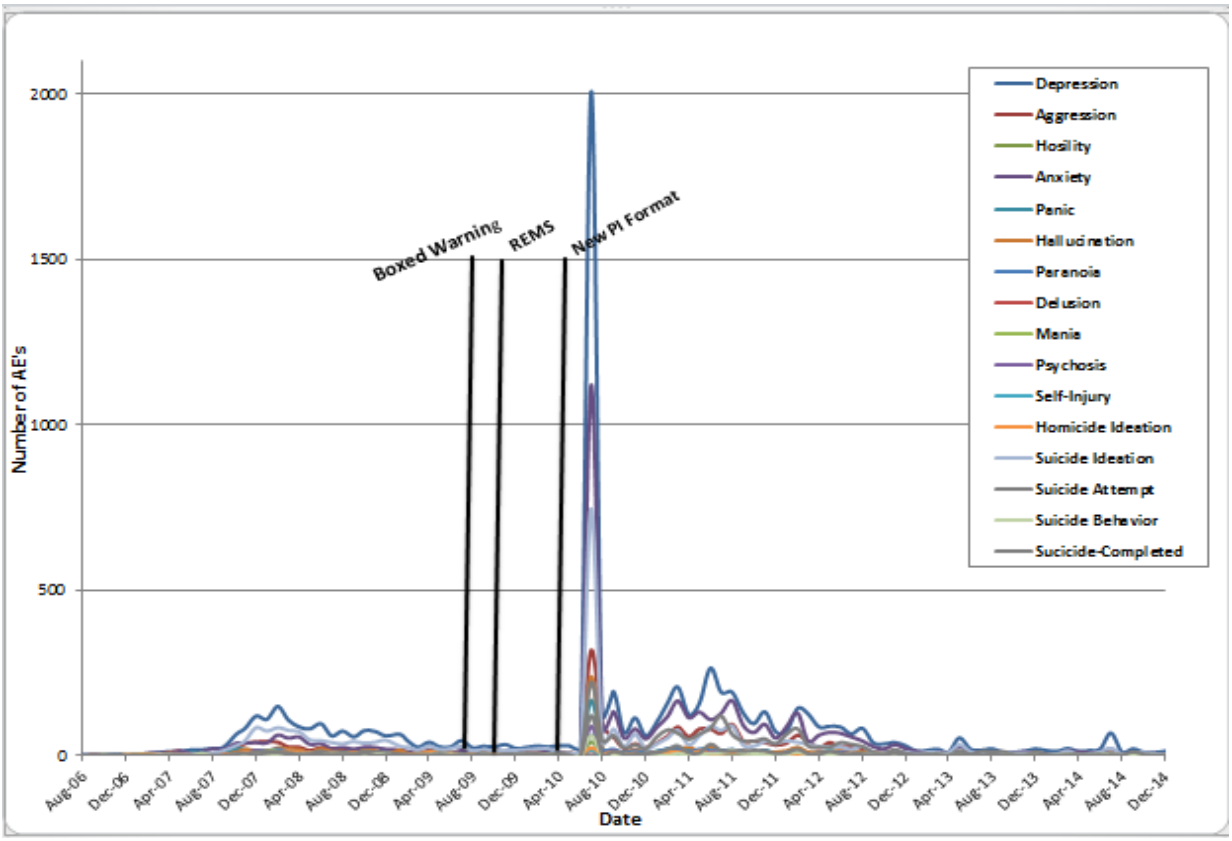

Figure 2: The number of adverse events for each of the serious neuropsychiatric adverse events over months from August 2006 through December, 2014.

Discussion

All adverse events seem to track together. In other words, they all seem to decrease and increase together, causing relatively the same pattern for all of the sixteen serious neuropsychiatric adverse events. The graph has a large peak in July, 2010 which contains most of the serious adverse events data. The reason for why this month contained the most data is explained in the next section. The three important FDA actions seem to have had no effect on the number of reported AEs. There is no observable change that can be attributed to these actions. The actions that the FDA mandated seem to have been ineffective with regards to decreasing the number of serious adverse events reports.

July 2010

As seen in Figures 1 and 2, July 2010 had the most data out of all of the months included in the graph. This month had a total of 5,277 serious adverse events reported from a total of 3,830 individual cases involving one or more of the serious neuropsychiatric adverse events specified above. The reason for the influx in the amount of data is that at the FDA's request Pfizer resubmitted a large number of adverse events reports that were "initially sent to the Agency in a way that did not allow for comprehensive evaluation". These reports were spread out over a number of years and had been sent to the FDA periodically in summary safety reports. ("FDA," 2011) According to an analysis performed by the ISMP, 12 of these cases were from 2006, 119 cases from 2007, 176 additional cases from 2008 and 589 cases were from 2009 and early 2010. **("**ISMP," 2011) Nonetheless, these reports confirmed what the Agency already

knew about the drug as they were consistent with the events that to led to the 2009 boxed warning.

The ISMP report discusses 896 reports, and based on the data tabulated in this study there were 3,830 individual cases for July 2010. The remaining 2934 cases contain different AE's then the specific AE's on which the ISMP focused. The ISMP had specific AE categories that they analyzed, including suicide related events, aggression/hostility, depression and psychosis. While this study accounts for a larger list of AE's, hence the larger number of AE's found for July 2010. If the actual dates of these cases were re-allocated, the results of the graph may be very different from the results in Figures 1 and 2. In other words, it may be possible that the FDA action did in fact have some effect on decreasing the number of AE's.

How effective were the FDA actions?

According to the frequency of reports by month, the FDA actions did not seem to have any effect on decreasing the number of serious adverse event reports. Changing the format of the drugs labeling, requiring the boxed warning and the medication guide did not have an effect on the number of serious adverse events reported. After seeing that the FDA's highest form of warning, the boxed warning was not effective, some hold the view that these actions were not enough protection for the consumer and would go as far as recommending that Chantix be removed from the market altogether. Those who hold this point of view argue that the boxed warning would not work for Chantix because a boxed warning is only effective in three situations in which Chantix does not apply to.

The first situation is that if side effects are detected early enough serious consequences can be prevented. For an example, in a situation where a drug can cause liver damage, the physician can monitor the patient's liver enzymes for evidence of liver injury and order the patient to stop taking the medication. The argument is that Chantix cannot be applied to this situation since "suicide occurrence" (one of the risks being warned about in the boxed warning), cannot be monitored for since it comes without prior warning and a depressed patient cannot be relied upon to communicate such symptoms to their physicians because of their condition. (Siegel, 2011) The second situation that Dr. Siegel (2011) argues is appropriate for a boxed warning is when certain serious adverse events tend to only occur in certain patients, in which the physicians can refrain from prescribing the drug to those patients whose specific health condition puts them at risk. For Chantix, however these neuropsychiatric side effects (including suicidal behavior and ideation) are not predictable based on previous psychiatric history. Finally, the third situation in which a boxed warning is useful is when the benefit of the drug far outweighs the drugs risk for an individual patient; that is where the drug is the only effective option available for the patient. And according to Dr. Siegel and those who share his views, Chantix is not the most effective drug in aiding patients with smoking cessation and that other alternative such as nicotine replacement therapies are just as effective. In other words, the risk associated with this drug is not worth taking. (2011)

Limitations

This research has several limitations. The first deals with the FAERS database itself from which the serious adverse events were obtained. There is no certainty that the reported AEs were actually due to the product. They may be due to causes other than the

drug itself. In other words; these serious adverse events may be due to nicotine withdrawal or may be attributed to concomitant medications such as antidepressant or antipsychotic medications. Also, the data do not account for all the actual serious adverse event cases associated with Chantix, as reporting adverse events to the FDA's database is voluntarily. As a matter of fact, it is estimated that less than 10 percent of all adverse events are being recorded into the database. ("GAO," 2010) In addition, some of these cases may be duplicate cases (several reports on an individual patient received from more than one source). Because it was not possible to determine if a case is a duplicate case, all cases that contained any of the specified neuropsychiatric AE's were counted. Lastly, the biggest limitation in this study is not knowing the actual date on which the AE's occurred. If the actual date on which the AE's occurred was known, the results may have been different than the ones obtained in this study and may present a trend that can suggest that the FDA actions did have an effect on decreasing the number of AE reports.

Future Direction

This researcher believes that Chantix should not be removed from the market despite the serious neuropsychiatric adverse events which were the subject of this research. Chantix should stay on the market because it is currently one of only two non-nicotine approved product for smoking cessation. The other products available for smoking cessation are Zyban, an anti-depressant that can be used to aid in quitting smoking, and nicotine replacement therapies (NTR's) such as nicotine patches, gum, inhalers etc. Zyban works best if it used in combination with NTR's. Chantix, however, more than doubles a person's chance of successfully quitting smoking and has been proven to be the

best smoking cessation product in preventing relapse and withdrawal symptoms. (Thompson, 2011)

The neuropsychiatric AE concerns may be controlled with the FDA and Pfizer continuously monitoring the drug. The FDA and Pfizer should continue their efforts in informing physician and consumers on any new information that becomes available regarding this drug, especially the risks associated with its use. At this point, after the FDA has taken all the actions in its authority short of withdrawing the drug from the market, the responsibility in my view rests on the individual patient. With any drug, patients should be careful enough to weigh the risks and benefits after being counseled and informed by their physicians, assuming that physicians are following the FDA's warning and updates about the drug. In addition to this, further measures should be taken to educate physicians so that they may restrict prescribing this drug to patient populations whose medical condition puts them at the greatest risk.

Conclusion

The new labeling format that follows the PLR, the boxed warning and the REMS in the form of a medication guide did not seem to have any effect on decreasing the reports of serious neuropsychiatric adverse events associated with Chantix.

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APPENDIX

Appendix A: Chantix's labeling information

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021928s033s034s037lbl.pdf

Appendix B: Chantix's Medication Guide

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021928s033s034s037lbl.pdf