

Varenicline: Where are we today?

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Introduction

In 2006, Chantix (varenicline) splashed boldly onto the nicotine cessation medication scene with full Food and Drug Administration (FDA) approval following the completion of three distinct Pfizer-funded clinical trials (Jorenby et al., 2006; Gonzales et al., 2006; Tonstad et al., 2006). Almost immediately, however, and contrary to the initial findings supporting the safety and efficacy of varenicline, news reports and other information began to surface asserting that this new smoking cessation aid appeared to have some serious psychiatric side effects (ABC Good Morning America, 2007; Moore, Cohen, Furberg, 2008). These reports along with others prompted the FDA in November of 2007 to impose requirements for the addition of specific warnings and patient instructions on Chantix. In 2009, a black box warning was placed on varenicline (FDA, 2007; FDA, 2009). Pfizer had once envisioned Chantix taking its place alongside the pantheon of the drug maker's other highly successful products, Lipitor, Celebrex, and Viagra. Instead, Chantix sales declined 15% to \$155 million by the third quarter in 2009 (Pierson, Berkrot, 2010); and lawsuits have proliferated (Faulk, 2012). And just when we thought that we knew all about varenicline and contrary to the clinical trial that found no elevated cardiovascular risk compared to placebo (Rigotti, 2010), Sonal Singh and colleagues published the results of a meta-analysis reporting that the cardiovascular side effects for this medication were much greater than previously reported (Singh et al., 2011). Yet within eight months of the Singh study, researchers at the University of California San Francisco (UCSF) also published a meta-analysis of their own showing that varenicline did not have significant or clinically meaningful cardiovascular risks associated with its use (Prochaska and Hilton, 2012). These authors challenged the methods of the Singh meta-analysis and thus threw into doubt the previous findings. And as the Singh / Prochaska debate continues, investigators across the country continue to publish clinical trials results that show that varenicline is safe and efficacious among most populations (Williams et al, 2012; Wong et al., 2012; Pachas et al., 2012).

All of these recently published studies really beg the question: Varenicline, where are we today? Some are saying that the jury is still out, while many others maintain that the existing warnings are sufficient and that varenicline can be used effectively to treat nicotine addiction. In this brief report, we describe the past and current status of varenicline from a range of perspectives. We trace its history and the apparent rise of associated psychiatric events reported by the drug maker leading to the FDA warnings. We re-examine and identify the key issues in the debate surrounding the Singh and Prochaska meta-analyses. We describe legal environment and some of the lawsuits associated with Chantix. Finally, we examine the Tobacco-Related Disease Research Program's (TRDRP) grant funding and program activities in this area, highlighting the upcoming live webcast, Varenicline: Where are we today?

Varenicline; Novel Smoking Cessation Aid

Varenicline tartrate, sold as Chantix in the United States and Champix in Europe is a smoking cessation drug that has gained wide use and at the same time generated much controversy. In February 2006, the Food and Drug Administration gave varenicline a “priority review” by shortening the standard ten-month period of review to only six months because ongoing clinical trials were showing the drug to be safe and effective. One of three initial clinical trials found that varenicline had significantly higher smoking abstinence rates than either bupropion (Zyban) or placebo (Jorenby, et al., 2006). The authors of the study stated that, “the most common adverse event was nausea” and overall that, “Varenicline is an efficacious, safe, and well-tolerated smoking cessation pharmacotherapy” (Jorenby, et al., 2006). In another Chantix Clinical trial, Gonzales and his team, reported in the Journal of the American Medical Association that: “Varenicline was significantly more efficacious than placebo for smoking cessation at all time points and significantly more efficacious than bupropion SR at the end of 12 weeks of drug treatment and at 24 weeks” (Gonzales, et al., 2006). Similarly, Tonstad and colleagues reported that, “Smokers . . . showed significantly greater continuous abstinence in weeks 13 to 24 compared with placebo. Continuous abstinence was maintained through the non-treatment follow-up through week 52” (Tonstad, et al., 2006). Findings from these trials were further supported by other studies; see for example Reus et al., 2007 and Hays, et al., 2008.

Varenicline is a novel smoking cessation aid in that it is non-nicotine based and works primarily on the $\alpha 4\beta 2$ nicotinic receptor in the brain. Varenicline partially stimulates these receptors, occasioning dopamine release and in doing so decreases cravings for nicotine. Additionally, when varenicline occupies the nicotinic receptors it blocks the reinforcing effects of smoking and helps prevent relapse after quit attempts. In this regard, varenicline is a partial agonist that allows the release of a small amount of dopamine, while at the same time it binds to neuronal receptors to block attachment by nicotine. This novel property was first discovered in the Pfizer labs using animal models in tests using cystisine, the chemical from which varenicline is derived (Coe, et al., 2005).

Following the above-mentioned successful clinical trials and subsequent FDA approval, varenicline, became widely available for use by clinicians in smoking cessation, taking its place alongside bupropion and nicotine replacement therapy (NRT). Despite the initial enthusiasm, however, some investigators began to raise cautionary flags. Klesges and colleagues, in a JAMA editorial from 2006 titled, “Varenicline for smoking cessation definite promise, but no panacea,” cautioned that compliance levels were likely to be different in real world settings than in academic medical centers. Furthermore, they noted, “the adverse effect profile of varenicline revealed that nearly 30% of participants reported nausea, a rate significantly higher than with either bupropion or placebo”. Additionally, “abnormal dreams were common and much more likely in the varenicline group” (Klesges et al., 2006). It is also important to note that these side effects had been reported by the clinical trials mentioned above.

Varenicline; the Gathering Storm: Psychiatric Side Effects

By November 2007, the FDA issued an “Early Communication about an Ongoing Safety Review of varenicline (marketed as Chantix)” (FDA, 2007). The FDA reported that they had received “reports of suicidal thoughts and aggressive and erratic behavior in patients who have taken Chantix, a smoking cessation product” (FDA, 2007). Many of the reports the FDA was

responding to were both from Pfizer and independent groups. By May 2008, Pfizer had updated its website and materials to alert customers that, “Some people have had changes in behavior, hostility, agitation, depressed mood, suicidal thoughts or actions while using CHANTIX” (Chantix.com, 2008). Indeed, by 2009 reports of side effects had become numerous enough and covered such a wide range of conditions, including cardiovascular events, diabetes, renal failure and certain drug interactions that the FDA determined that it was necessary for Pfizer to place a black box warning on Chantix products and to inform caregivers and patients about the warnings (FDA, 2009).

Other health-related groups following the developments on varenicline initiated their own investigations on the medication’s safety and efficacy. One of these groups, the Institute for Safe Medication Practices (ISMP), a non-profit organized to educate the healthcare community, conducted a retrospective analysis on consumer calls and other reports to the FDA concerning varenicline. They reported that by the latter part of 2007, varenicline accounted for 988 serious injuries in the U.S. reported to the FDA, more than any other individual drug in this period. By comparison, the FDA received a median of five reports of serious injury for 769 different drugs in same period. Only 35 drugs accounted for 100 or more reports” (Moore, Cohen, Furberg, 2008).

Following this report, Thomas Moore, the lead author on the above mentioned study, published another retrospective review of the FDA Adverse Event Reporting system from 1998 to 2010 finding that of the 3,249 reported cases of suicidal/self injurious behavior or depression, 2,925 or 90% were attributed to varenicline, only 229 or 7% to bupropion and, 95 or 3% to NRT (Moore, et al., 2011). It should be noted that both in the ISMP report and the PloS ONE publication, the data are raw numbers, and do not take into consideration the actual overall volume of prescriptions, reports, and inquiries for varenicline during this time period compared with other FDA approved smoking cessation medications. Despite this, Dr. Curt Furberg, a professor of public health sciences at Wake Forest Baptist Medical Center and a co-author of the above mentioned study told ABC news that: "The FDA's own data show that Chantix is more dangerous than other treatments to stop smoking," (ABC News, 2011).

In response to the Moore et al., article Pfizer issued a press release questioning the author’s methods:

“The analysis by Moore et al is based solely on post-marketing reports of adverse events that have been available to the FDA for some time. Post marketing reports do not establish a cause and effect relationship between a medicine and a reported adverse event. These reports can come from any source ranging from patients to healthcare providers, and from phone calls to internet postings. Often these reports lack sufficient medical information to enable a meaningful assessment. Due to these limitations, any conclusions based on comparisons between different drugs and reporting rates are not reliable” (Pfizer, 2011).

Still, in reaction to the Moore report and the continuing negative press for Chantix, the FDA conducted two observational studies among Chantix users at the Veteran’s Administration and the Department of Defense. Of the more than 60,000 cases reviewed in these retrospective assessments, the studies found only 71 psychiatric hospitalizations and that these hospitalizations

were no more common in varenicline users compared to nicotine replacement users (Silverman, 2012). These findings however, did not end the controversy, rather lawsuits continued to be filed against Pfizer (see below) and other potential side effects emerged. As for this latter point, a study conducted by Rigotti, et al., and published in 2010, found that: “Varenicline is effective for smoking cessation in smokers with cardiovascular disease. It was well tolerated and did not increase cardiovascular events or mortality; however, trial size and duration limit definitive conclusions about safety” (Rigotti, et al., 2010). This latter concern about safety, coupled with continuing reports of potential varenicline side effects, prompted the FDA, a year and a half later in June of 2011, to post the following on its website:

“**[6-16-2011]** The U.S. Food and Drug Administration (FDA) is notifying the public that the smoking cessation aid Chantix (varenicline) may be associated with a small, increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. This safety information will be added to the *Warnings and Precautions* section of the Chantix physician labeling. The patient Medication Guide will also be revised to inform patients about this possible risk.” (FDA, 2011)

A closer look at the FDA website’s evidence shows that it was drawn from the Rigotti study. Despite the authors of that study stating clear limitations to any conclusions about safety (Rigotti, 2010), the FDA appeared to have determined that it was necessary to alert the public of the possibility of the small increased risk (FDA, 2011). One of the authors on the Rigotti Study, Dr. Neal Benowitz, will be a panelist on the TRDRP live webcast: Varenicline: Where are we today? (See below).

In Addition, Cardiovascular Side Effects, too? Sonal vs. Prochaska

In July of 2011, the scientific debate on the cardiovascular side effects of varenicline was taken to a new level when Dr. Sonal Singh at Johns Hopkins’s School of Medicine and colleagues published results from a meta-analysis in the Canadian Medical Association Journal (Singh, et al 2012). The authors reported that based on the analysis of 14 double-blind, randomized controlled trials that involved 8,216 patients and ranged in duration from 7 to 52 weeks, a significantly increased risk of serious cardiovascular adverse events was associated with varenicline – “1.06 percent in varenicline versus 0.82 percent in placebo group; Peto odds ratio [OR] 1.72, 95% confidence interval 1.09-2.71” (Singh, et al, 2011). Said another way, the authors reported that varenicline was associated with a 72% increased risk of serious adverse cardiac events including myocardial infarction, stroke and cardiovascular-related death. It should be noted that along with this publication, a number of brief commentaries were included in the CMAJ issue that published the Singh study questioning some of the methods used by Singh and colleagues. Of particular note, are the comments by Taylor Hays, Professor of Medicine at the Mayo Clinic, who was also the second author on Jorenby clinical trial. His remarks foreshadow many of the points that would be made by Drs. Judith Prochaska and Joan Hilton at the University of California San Francisco some eight months later. Hays pointed out that Singh’s findings must be tempered by the rarity of these events among participants in both treatment groups of 1.06% among patients given varenicline and 0.82% among patients given a placebo — an absolute percent difference of only 0.24% (Hays, 2011). Hays concluded that:

“Although their results suggest that a measure of caution should be taken in prescribing varenicline for the treatment of tobacco dependence, the small absolute risk of cardiovascular events associated with taking varenicline is outweighed by the enormous benefit of reducing cardiovascular morbidity and mortality that can be achieved with successful abstinence from smoking” (Hays, 2011).

The initial methodological concerns with the Singh study gave way to a full review and meta-analysis by Prochaska and Hilton of 22 trials that used varenicline as a smoking cessation aid, encompassing 9,232 participants. In their review, they found a difference in risk of serious cardiovascular events was only 0.27 percent between those on Chantix versus placebo, which was not clinically or statistically significant (Prochaska and Hilton, 2012). The authors identified a number of methodological issues they suggest that led Singh and colleagues astray. First, they questioned Singh’s inclusion of adverse events that were well beyond the treatment period. Second, Singh and colleagues excluded trials where there were no cardiovascular events and in doing so biased findings against the null hypothesis (i.e., of no cardiovascular risk). Third, Prochaska and Hilton voiced concern about Singh’s use of the Peto odds ratio, “which has shown bias under conditions of imbalanced design and rare events, which were present in most of the reviewed trials” (Prochaska and Hilton, 2012). Fourth, the UCSF authors were concerned that in most of the studies reviewed by Singh, retention was lower in the placebo group, thus reducing the likelihood of detecting adverse events in that arm of the study. This latter point was noted in Hays’ commentary when the Singh study was first published (Hays, 2011).

Singh responded to one of the UCSF researchers concerns about including events beyond the treatment period. In an interview by *Pharmalot* (Ed Silverman’s blog on the pharmaceutical industry), Singh stated that, “what remains unknown is the length of time that a heart risk may appear after treatment ends. We were learning from the Vioxx issues. With Vioxx, heart risks didn’t climb until long after people were taken off the drug” (*Pharmalot*, 2012). In a formal response to the UCSF study, Singh and the second author on the CMAJ article, Dr. Yoon Loke from the University of East Anglia in the United Kingdom stated that Prochaska and Hilton had excluded a number of cardiovascular events from their review. Second, because Singh and team were using intent-to-treat analysis, the non-compliance of placebo or varenicline group is not relevant. Third, Loke quotes the Cochrane hand book that the Peto odds ratio, “method was found to be the least biased and most powerful method, and that risk difference analytical methods tended to show conservative confidence interval coverage and low statistical power when risks of events were low” (Singh, 2012).

This debate is ongoing and goes to the core of how meta-analysis is used to assess risk. Drs. Singh and Prochaska will be participating in the upcoming TRDRP-sponsored live webcast to discuss this issue (see below)

Drug Maker Sued, and Sued, and then Sued Some More

Chantix has generated thousands of personal injury and product liability lawsuits for Pfizer, none of which has yet to be settled. Indeed, as of March 2012, nearly 2,500 (2,498) individuals and companies have brought lawsuits against Pfizer concerning Chantix (Faulk, 2012). The cases cited below are a sampling of what has become, one could argue, a cottage industry. For example, in September of 2007 the parents of Carter Albrecht filed suit against Pfizer for alleging that Pfizer had not disclosed neuropsychiatric risks associated with Chantix and that the

company failed to warn users of possible side effects adequately. Filed in Dallas, Texas, the suit claims that once Carter started taking Chantix he became violent, confused and at times terrified. Carter was shot to death by his neighbor, after he [Carter] violently banged on the neighbor's door (Lawyersandsettlement.com, 2012). A subsequent blood test showed that Carter was intoxicated, with a blood alcohol level 3 times the legal limit (Eiserer, 2007). Also in 2007, Judy Whitley who alleges that her husband committed suicide after taking Chantix filed another suit in Minnesota (Gibb 2012).

By 2008, the law firm Sanders, Viener and Grossman LLP had filed five separate product liability lawsuits against Pfizer in New York State, alleging that each of the plaintiffs either committed suicide or attempted suicide while suffering under the neuropsychiatric side effects of Chantix (The Sanders Firm, 2012). In 2010, three personal injury lawsuits were filed against Pfizer in New York Superior Court by the same law firm (The Sanders Firm, 2012). These lawsuits claim that Pfizer had failed to inform doctors about the dangers associated with Chantix and that the drug's labeling was inadequate. In two of the lawsuits filed, plaintiffs claim that taking Chantix led them to attempt suicide while in the third case; wrongful death is claimed for an Indiana woman who committed suicide after using Chantix (The Sanders Firm, 2012).

Indeed, cases became so numerous and multiplied nationwide across the country so quickly that the United States Judicial Panel on Multidistrict Litigation grouped all these cases together and in 2009 assigned them to the U.S. District Judge for Northern Alabama, Inge Johnson. Judge Johnson has selected eight cases to be bellwethers, that is, test cases in the litigation against Pfizer. He has grouped them in discrete groups, starting with the suicide cases then moving to the suicidal ideation cases. The first case is scheduled for trial on October 22, 2012 (Faulk, 2012).

As these lawsuits make their way through the legal system, the drug maker continues to maintain the safety and efficacy of its smoking cessation drug stating that, "Pfizer stands by Chantix which is an effective treatment option for adult smokers who want to quit and has been approved in 100 countries and prescribed to 15 million smokers, including 8 million in the United States." Pfizer continues stating that, "to date, Chantix has been studied in more than 8,000 smokers, including 30 randomized controlled clinical trials...and none of these studies have found reliable scientific evidence that Chantix causes the neuropsychiatric events alleged in these lawsuits" (Pfizer, 2011). Currently, Pfizer at the behest of the FDA is conducting large double-blind placebo control safety trial among patients with and without psychiatric disorders. Results of this trial are expected in 2017 (Pfizer, 2011).

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Pfizer is not alone in maintaining the safety of Chantix. The FDA continues to consider this drug, if the proper precautions are taken, to be an effective smoking cessation drug (FDA, 2012). In fact, published clinical trials continue to support Pfizer's claims of the safety and efficacy of Chantix. For example, Dr. Jean Wong and her team conducted a study on 286 patients to determine the efficacy and safety of a perioperative smoking cessation intervention with varenicline vs. placebo. These investigators found that: "A perioperative smoking cessation intervention with varenicline increased abstinence from smoking 3, 6, and 12 months after elective non-cardiac surgery with no increase in serious adverse events" (Wong et al., 2012).

Similarly, Jill Williams and her group found that among patients with schizophrenia that, “Varenicline was well tolerated, with no evidence of exacerbation of symptoms, and was associated with significantly higher smoking cessation rates versus placebo at 12 weeks. Our findings suggest varenicline is a suitable smoking cessation therapy for patients with schizophrenia or schizoaffective disorder” (Williams, 2012). In still another recently published clinical trial among patients diagnosed with schizophrenia, Pachas and colleagues found that varenicline: “may be well-tolerated and effective for smoking cessation in combination with group CBT [Cognitive Behavioral Therapy] in stable outpatients with schizophrenia, a group with high rates of smoking and smoking-attributable morbidity and mortality” (Pachas, 2012). Dr. Eden Evins, an author on the study will join the TRDRP’s live webcast (see below) to talk about varenicline and potential psychiatric co-morbidities.

Even after numerous trials continue to support the safety and efficacy of varenicline, concerns and controversy still surrounds this drug prompting some federal agencies to distance themselves and their employees from the use of this product. In 2008, the U.S. Federal Aviation Administration banned commercial pilots from using Chantix after the ISMP report asserted that the drug was linked to blackouts and vision problems (Wood, 2008). Additionally the Federal Motor Safety Administration (which oversees interstate commerce) followed suit and issued “a warning advising medical examiners to not qualify anyone currently using varenicline for commercial motor vehicle licenses” (Wood, 2008). The Department of Veterans Affairs has also limited the use of Chantix, stating: “Varenicline is a second-line medication for smoking cessation in the VA health care system and should be used only for those patients who have failed an appropriate trial of nicotine replacement therapy, bupropion, or combination therapy...within the past year” (Veterans Administration, 2008, updated 2011). While some commentators argue that the standard of practice should follow the recommendation of the U.S. Veterans Administration (Moore et al., 2011), it should be borne in mind that all clinical trials reviewed for this article supports Pfizer’s claim of the efficacy and safety of varenicline/Chantix. Only the Moore, et al., retrospective analysis of the FDA Adverse Event Reporting System and the Singh et al. meta-analysis coupled with individual reports have continued to raise some concerns about this drug; thus begging the question: Varenicline: Where are we Today?

To address this question, the Tobacco Related Disease Research Program (TRDRP) is hosting a live Webcast titled: Varenicline: Where are we today? **This interactive webcast will take place on Thursday, September 20, 2012 at 10:00 a.m. PDT.** A panel of experts will examine the issue surrounding the debate about varenicline and give their assessment of where we are today with this drug. Panelists are Drs. Neal Benowitz, University of California San Francisco; Eden Evins, Harvard University; Judith Prochaska, Stanford University; and Sonal Singh, Johns Hopkins University. Information about how to join the webinar is posted on the TRDRP web page devoted to [Varenicline](#).

In the future, TRDRP plans to host other live webcasts on *Burning Issues* related to tobacco-related disease and tobacco control research. These webcasts will identify critical questions facing tobacco-related disease science and tobacco control, convene experts on the topic, and host a nationwide discussion on these matters.

The TRDRP has been supporting research on varenicline for some time now. In the program's 2012 and 2013 Call for Applications, investigators were invited to apply for grants and conduct studies that: "Improve the efficacy of varenicline and/or develop more efficacious partial agonists." In a currently funded study, Dr. Dennis Dougherty suggests that, "One strategy to developing new smoking cessation drugs is to develop molecules that target the same receptors as nicotine, but that do not activate them in the same way. In this way, the drugs interfere with nicotine's actions and negate its addictive properties. The smoking cessation drug Chantix is the first pharmaceutical to work in this way, but, in part because of associated side effects, improved versions of this drug would be of great interest" (Dougherty, 2010). In another TRDRP-funded study, Dr. Tanuja Bordia, working along with his colleague Dr. Maryka Quik at SRI International, has established that varenicline not only activates the $\alpha 4\beta 2$ nicotine receptor, but also activates the $\alpha 6\beta 2$ receptor; this ability of varenicline to activate numerous receptors in the brain may be in part responsible for Chantix's efficacy (Bordia, 2012).

From the research perspective, we see that the scientific evidence supports the efficacy of varenicline for smoking cessation and continuous abstinence. On the other hand, lawsuits continue to proliferate and the perception among the public and media is that varenicline comes with psychiatric and cardiovascular risks. The presentations in the "Varenicline: Where are we Today?" panel and live webcast will further elucidate science underlying the claimed safety and efficacy of this smoking cessation aid. Chantix was the first smoking cessation aid of its kind, and probably will not be the last.

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