Smoking Cessation: Initial Insights into a New Drug

Binu Krishnan

Department of Pulmonary and Critical care and Sleep Medicine, PRS Hospital, Thiruvananthapuram.*

ABSTRACT

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Varenicline is a nicotinic receptor partial agonist (α4β2 subtype) suggested to be used in smoking cessation. Initial trials with this drug show a much higher response than the currently available alternatives. Though the most common adverse event is nausea, concerns have been raised about the possible neuropsychiatric complications of this molecule. Also, the possibility of physical dependence needs to be further evaluated.

Keywords: Varenicline, Nicotine, Champix

*See End Note for complete author details

INTRODUCTION

Varenicline (trade name Chantix in the USA and Champix in Europe and other countries, marketed by Pfizer, as Varenicline tartrate) is a prescription medication used to treat smoking addiction. Varenicline received a "priority review" by the U.S. Food and Drug Administration in February 2006, shortening the usual 10-month review period to 6 months because of its demonstrated effectiveness in clinical trials and perceived lack of safety issues.[1] The agency's approval of the drug came on May 11, 2006.[2] From August 1, 2006, Varenicline has been available for sale in the United States, and on September 29, 2006, it was approved for sale in the European Union. Interestingly, the FDA refused to approve Pfizer's use of the name "Champix" asserting that from a promotional perspective, "it is overly fanciful and overstates the efficacy of the product"

MECHANISM OF ACTION

Varenicline is a nicotinic receptor partial agonist (α4β2 subtype). It is different from nicotinic antagonist, bupropion, and nicotine replacement therapies (NRTs) like nicotine patches (commonly, "the patch") and nicotine gum. As a partial agonist, it both reduces cravings for and decreases the pleasurable effects of cigarettes and other tobacco products.[3]

Most of the active compound is excreted renally (92-93%). The elimination half-life is about 24 hours.[4]

Indications

Varenicline is suggested for use in smoking cessation. It is an alternative to NRTs and has demonstrated greater efficacy than them in comparable studies.[5] The FDA has approved its use for twelve weeks. If smoking cessation has been achieved it may be continued for another twelve weeks.[2] Varenicline has not been tested in children, those under 18 years old, or pregnant women, and therefore is not recommended for use by these groups. Women currently breastfeeding should also avoid this product, since Varenicline may pass into the breast milk, leading to unknown effects on the child.

Currently available alternatives

Chantix entered the quitting product market as a prescription aid at a time when NRT was the clear frontrunner. Nicotine gum was first approved by the FDA

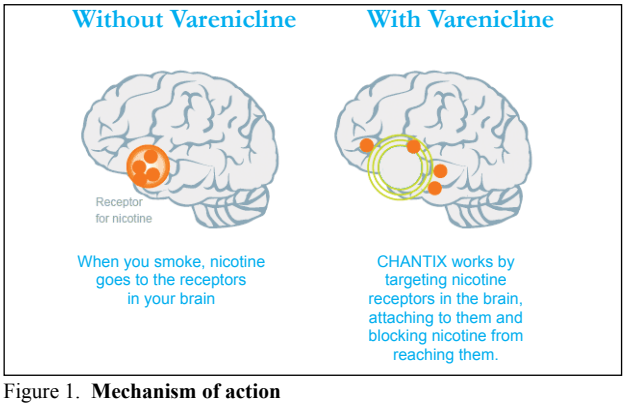

Figure 1. **Mechanism of action**

Corresponding Author:
Dr. Binu Krishnan, MD, DTCD, Consultant Pulmonologist, Pulmonary, Critical care and Sleep Medicine, PRS Hospital, Thiruvananthapuram. Phone: 9847591396, Email: binukrishnanck@hotmail.com

for prescription use in 1984 and was followed by the nicotine patch in 1991. Both the gum and patch were approved for over-the-counter (OTC) sales in 1996, the same year when prescription nicotine nasal spray was approved. The nicotine inhaler and bupropion (Zyban) joined as prescription products in 1997. In 2002 the lozenge became the first nicotine delivery device to enter the market directly as an OTC product. Initial studies of gums and patch, like Pfizer's Champix studies, were often loaded with education, counseling and support elements.

Varenicline's 22% one-year rate is actually lower than the 1976 nicotine gum study headed by Russell[6] in which 23% were still not smoking at one year. It also fails to measure up to the 1980 Raw[7] study which produced a whopping 38% one-year rate, to the 1982 Jarvis8 study's 31%, the 1983 Schneider[9] study with 30%, the 1984 Hialmarson study at 29%, or the 1989 Tonnesen[10,11] study which boasted a 44% one-year quit rate.

Trials

Pfizer's five clinical trials of Varenicline were published in July and August 2006. Three are comparable in that they involved a 12-week treatment period using 1mg of Varenicline twice daily. The study headed by Gonzales[12] produced a 21.9% one year Champix quit smoking rate, in Oncken[13] the rate was 22.4% and in Jorenby[5] 23% - an average of 22%. Varenicline/Nicotine Patch Study (2008) by Aubin[14] et al, 2008 - This 52 week study compared 12 weeks of Varenicline (1mg twice daily) by 376 users to 10 weeks of stepped-down nicotine patch use (21mg to 7mg patches) by 370 patch users. The week 52 abstinence rate (NRT, weeks 8–52; Varenicline, weeks 9–52) was 26.1% for Varenicline and 20.3% for NRT (OR 1.40, 95% CI 0.99 to 1.99, p=0.056). Varenicline significantly reduced craving (p, 0.001), withdrawal symptoms (p,0.001) and smoking satisfaction (p,0.001) compared with NRT. The most frequent adverse event was nausea (Varenicline, 37.2%; NRT, 9.7%).

Though it is claimed that after 12 weeks, the abstinence rate is 44%, only time will tell whether this will come down in the subsequent trials.

Also, these rates were achieved under highly artificial clinic study conditions. Pfizer spared no expense in creating one of the most intense clinic quitting experiences in any smoking cessation study ever.

Real-world quitters, alone with their Champix pills, or even participating in Pfizer's Get Quit support plan, will be fighting under entirely different battlefield conditions. Varenicline study participants received a free 12-week supply of Champix, were reimbursed travel expenses associated with visiting their health provider to obtain it, attended 16 clinic visits involving one-on-one sessions lasting up to 10 minutes, with counselors trained in motivation and coping skills development, and received 8 follow-up telephone support calls from their provider.

Adverse event profile:

Side Effects:

Nausea occurs commonly in people taking Varenicline. Other less common side effects include headache, difficulty in sleeping, and abnormal dreams. Rare side effects reported by people taking Varenicline compared to placebo include change in taste, vomiting, abdominal pain, flatulence, and constipation.[15]

In November 2007, the FDA announced it had received post-marketing reports that patients using Chantix for smoking cessation had experienced several serious symptoms, including suicidal ideation and occasional suicidal behavior, erratic behavior, and drowsiness. On February 1, 2008 the FDA issued an Alert to further clarify its findings, noting that "it appears increasingly likely that there is an association between Chantix and serious neuropsychiatric symptoms." It is unknown whether the psychiatric symptoms are related to the drug or to nicotine withdrawal symptoms, although not all patients had stopped smoking. The FDA is aware of the highly- publicized case of Carter Albrecht who, in an apparent state of delirium, was shot to death by his neighbor after hitting his girlfriend and then trying to forcibly enter the neighbor's house.16 Although in this case the delirium appeared to be caused by taking Varenicline with a high dose of alcohol, the FDA asked Pfizer for additional cases that might be similar. It also recommended that health care professionals and patients watch for behavioral and mood changes.

On Thursday, May 22, 2008, The New York Times reported that the U.S. Federal Aviation Administration (F.A.A.) had announced the day before a ban on the use of Chantix (Varenicline tartrate) for both pilots and air traffic controllers, due to concerns with possible adverse neuropsychiatric effects which could be detrimental to public safety.[17]

On Tuesday, June 17, 2008, The Washington Times reported on its Front Page that the United States Department of Veterans Affairs was testing Chantix on war veterans with Post Traumatic Stress Disorder without properly warning them of the side effects, and that in one case a veteran was almost killed when he had a psychotic episode and threatened police officers.[18]

From the above events, it is quite clear that psychiatric adverse events have to be further evaluated in the long run. This becomes all the more significant by the fact that at least 30% of current smokers may exhibit some forms of psychiatric disturbances.

DEPENDENCE

Dismal real-world NRT success rates have resulted in the industry actually blaming quitters for not using it properly. But proper use often results in the quitter getting hooked on the cure. In 2004 GlaxoSmithKline consultants noted that nearly 40% of nicotine gum users are dependent upon it, or, as the consultants like to put it, they've become "persistent users."

It is described that 'abrupt discontinuation of CHAMPIX was associated with an increase in irritability and sleep disturbance in upto 3% of subjects'.[19] Once 1 mg bd dosage is reached, there is no reduction or tapering of dose until the treatment is completed (whether it is at 12or 24 weeks). So if treatment stoppage at 12 or 24 weeks is not associated with any adverse effects, then how can 'abrupt discontinuation' cause such reactions? Again, this signifies the possibility of physical dependence which needs to be further evaluated.

Smokers who were excluded from trials Champix and Chantix's real-world performance rates are likely to be further eroded by the fact that a substantial percentage of difficult to treat smokers applied to participate in each study but were denied. In Gonzales 1,843 smokers were screened and 458 were excluded (25%), in Oncken 980 were screened and 333 excluded (34%), and in Jorenby[5] 1,413 were screened and 386 excluded (27%).

Most within these groups reflect populations that have historically been extremely challenging to assist in quitting, including youth who often smoke fewer than ten per day. Real-world conditions will not bar them from using Varenicline. Their use of Champix or Chantix has not yet been studied and we have no idea how their status and conditions will impact outcome.

CONCLUSION

A pack-a-day smoking habit at an average cost of Rs.40/day will cost a patient approximately Rs.14000 per year.[19] One can imagine the economic benefits for the individual and his community when that person quits smoking. Most of the smokers start their habit by early teenage. CHAMPIX is not tested to be suitable for that age. Hence a new drug has to emerge (or this drug has to be proven), which can arrest smoking habit at that age group itself. Overall, whether the benefits of this drug outweigh the risks (esp. neuropsychiatric) remains to be evaluated in the long term.

END NOTE

Author Information

Dr. Binu Krishnan, MD, DTCD,
Consultant Pulmonologist, Pulmonary,
Critical care and Sleep Medicine, PRS Hospital,
Thiruvananthapuram. Phone: 9847591396.
Email: binukrishnanck@hotmail.com

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