Review Article and Clinical Experience: VARENICLINE (CHAMPIX®) : A BREAKTHROUGH FOR SMOKING CESSATION TREATMENT (An α4ß2 Nicotinic Acethylcholine Receptor Partial Agonist)

Askandar Tjokroprawiro
Diabetes and Nutrition Centre
Dr. Soetomo Teaching Hospital,
Airlangga University School of Medicine, Surabaya

ABSTRACT

Tobacco is currently responsible for the death of one in ten adults in the world. Indonesia is also most prevalent for smoking with a total amount of smokers 62,800,000 people. Cigarette smoke contains gaseous compounds, one of which is nicotine, a compound that results in addiction. Nicotine produces neurochemical effects through six pathways. One of these is dopamine that produces the feeling of reward. Due its short half-life, withdrawal symptoms occur quickly, and results in relapses that reinforce the reward and satisfaction, which starts the addiction cycle. Varenicline (champix®), a selective α4ß2 nicotinic acethylcholine receptor (nAChR), is a drug for smoking cessation treatment. Varenicline is indicated for smokers (especially chain-smokers) in adults. The presence of varenicline is associated with lowered dopamine release level. Studies found that varenicline had an acceptable safety and well-tolerated. The majority of adverse events are reported to be of mild-to-moderate intensity. Health benefits of this drug starts immediately after cessation, and fifteen years afterwards, the CHD risk of the patient may be smaller to that of a non-smoker.

Keywords: *tobacco, cigarette smoke, nicotine, dopamine, smoking cessation, acethylcholine, varenicline (champix®)*

Correspondence: Askandar Tjokroprawiro, Diabetes and Nutrition Centre, Dr. Soetomo Teaching Hospital, Airlangga University School of Medicine, Jl Mayjen Mustopo 6-8, Surabaya, phone: 62-31-5501625
email: diabetes@rad.net.id

Abbreviations: **AEs** = adverse effects; **CAR** = continuous abstinence rate; **CO** = carbon monoxide; FDA = food drug administration; **nAcc** = nucleus accumbens; **nAChR** = nicotinic acethylcholine receptor; **NRT** = Nicotine Replacement Therapy; **VTA** = ventral tegmental area

INTRODUCTION

Tobacco is the second major cause of death in the world. It is currently responsible for the death of one in ten adults worldwide (about 5 million deaths per year). The big four countries which showed high smoking prevalence of men in Asia are (WHO 2002): Indonesia 69.0%, China 53.4%, Thailand (39.3%), and India 29.4%. Indonesia is the most prevalent for smoking with a total amount of smokers : 62,800,000 people or 69.04% men and 4.83% women. Cigarette smoke contains about 500 gaseous compounds and thousands of compounds in the particle phase. It also contains tar, which is containing various carcinogens, and alkaloids – nicotine, nor nicotine, anatabine, anabarasine. Nicotine ($C_{10}H_{12}N_2$) is thought to be component that results in addiction. Nicotine is rapidly absorbed (only 10-19 seconds to reach the brain) during cigarette smoking and produces its physiological and behavioural effects by binding to α4ß2 nAChRs subtype in the ventral tegmental area (VTA) as seen in Figure 1. Nicotine binding leads to the release of dopamine in the nucleus accumbens (nAcc), producing feeling of reward. Smokers therefore feel good (pleasure) when they smoke. However, as the half-life of nicotine is only 2 hours, withdrawal symptoms occur quickly. Withdrawal symptoms last for several weeks, but can be blunted by pharmacologic agents. Varenicline (champix®) is a novel drug for smoking cessation treatment. Varenicline, a selective α4ß2 nicotinic acethylcholine receptor (nAChR) partial agonist, can be used as a novel therapy for smoking cessation (FDA approval: 11 May 2006). The nAChR system in the VTA performs a pivotal role in nicotine reinforcement, mediated in particular by α4ß2 receptors.

THE PATHWAY: FROM NICOTINE - VTA - TO THE NUCLEUS ACCUMBENS

There are six pathways for neurochemical effects of nicotine from nicotine – VTA – to the nucleus

accumbens in the central neurons system (Figure 2). They are dopamine, which is associated with pleasure; norepinephrine, with appetite suppression; acethylcholine, with arousal and cognitive enhancement; vasopressin, with memory; serotonin, with mood modulation; and ß-endorphin, with anxiety reduction.

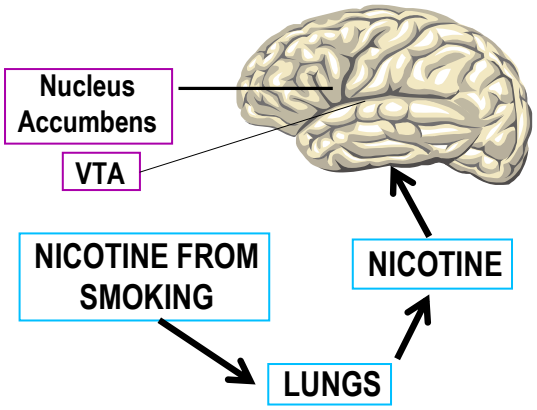

FIGURE – 1 Nicotine Addiction – Reinforcing Behavior

After inhalation, nicotine enters the brain in a matter of seconds (10-19 seconds) and binds predominantly to the α4β2 subtype of neuronal nicotine acethylcholine receptors (nAChRs).

Cravings for tobacco, together with withdrawal symptoms (for example, irritability, depressed mood, anxiety and insomnia) result in relapses that reinforce the reward and satisfaction from nicotine, starting the addiction cycle again. When sufficient nicotine is present in the blood to active α4ß2 nAChRs in the VTA, there is a burst firing of dopaninergic neurons in the mesolimbic projection to the nucleus accumbens (nAcc) inducing the increased release of extra-synaptic dopamine in the nAcc (Figure 2). Such an activity appears to be associated with the reinforcing and addictive properties of nicotine (Kelly 2002). When varenicline is present and activating α4ß2 nAChRs in the VTA, there is a lower level of sustained dopamine release in the nAcc (nucleus accumbens) relative to nicotine (Figure 2). Additionally, the presence of varenicline at α4ß2 nAChRs prevents nicotine from binding (Coe et al. 2005; Rollema et al. 2006).

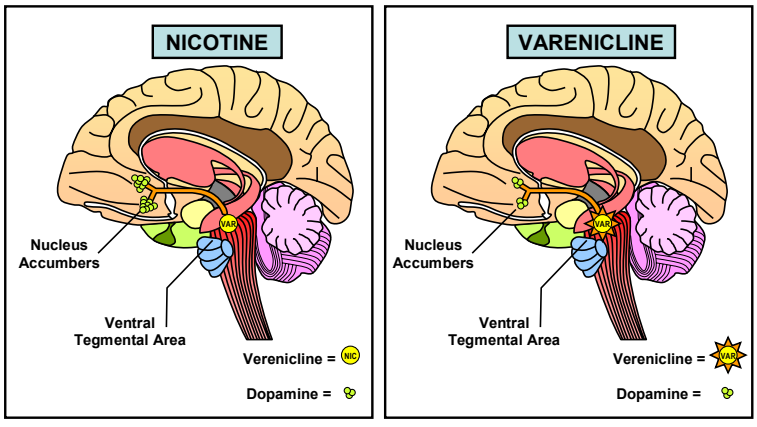

FIGURE-2 Pharmacokinetics of Varenicline

The two meta-analyses have made direct and indirect comparisons of varenicline versus placebo and other smoking cessation pharmacotherapies (Wu et al 2006, Cahill et al 2007). Every varenicline clinical trial reported in this section assesed smoking cessation based on self-reported abstinence (usually termed continuous abstinence rate = CAR) using a standard questionnaire, confirmed by end-expiratory carbon monoxide (CO) measurement of < 10 ppm and included non-treatment follow-up of smoking status to 1 (one) year.

In a trial (Jorenby et al 2006) that randomized 1027 participants to treatment medication, continuous abstinence rates (CARs) for varenicline were significantly greater for varenicline than for placebo or bupropion SR (for weeks 9-12), i.e., 43.9% for varenicline versus 17-6% for placebo (OR = 38.5; 95% CI = 2.69-5.50; p < 0.001) and 43.9% for varenicline versus 29.8% for bupropion SR (OR = 1.90; 95% CI = 1.38-2.62; p < 0.001). Continuous abstinence rates (CAR) remained significantly higher for varenicline for weeks 9-52, i.e., 23% for varenicline versus 10.3% for placebo (OR = 2.60; 95% CI = 1.72 – 4.11; p < 0.001) and 23% for varenicline versus 14.6% for bupropion SR (OR = 1.77; 95% CI = 1.19 – 2.63; p = 0.004).

PHARMACOKINETICS AND ADVERSE EVENTS OF VARENICLINE

In a recent trial (Williams et al 2007) assessing the long-term safety of varenicline, in which varenicline 1 mg b.i.d was administered for up to 1 (one) year, the most common adverse events (AEs) reported by participants were nausea (40.2%), abnormal dreams (22.7%) and insomnia (19.1%), with the majority reported to be of mild-to-moderate intensity. Overall, varenicline has an acceptable safety and is generally well tolerated for up to 1 (one) year. Adverse events of varenicline (champix®) that occurred in clinical studies more frequently than 5% and of placebo can be seen in Table 1.

TABLE -1 Adverse events of Varenicline that occurred in clinical studies more frequently than 5% and of placebo

Adverse Events	Champix®	Placebo
- Nausea	28.6%	8.8%
- Mild	71.5%	84.5%
- Moderate	24.7%	11.3%
Severe	3.8%	4.2%
Insomnia	15.5%	11.3%
Abnormal dreams	12.4%	4.5%
Headache	10.2%	8.7%
Constipation	5.8%	2.2%
Dry mouth	5.6%	4.1%
Dizziness	5.2%	4.6%
Flatulence	5.1%	2.5%

Pfizer Ltd Sandwich, UK (2006) has summarized the pharmacokinetics of varenicline. It has a half-life of 24 hours, and Cmax within 3 to 4 hours. Its steady-state is reached within 4 days, and its oral bioavailability is unaffected by food. Ninety-two percent of drug is excreted unchanged. There is no inhibition of cytochrome P450 enzymes, no clinically meaningful drug interactions identified, and no dose restrictions in patients with hepatic insufficiency. Dose adjustment required for severe renal impairment may be considered for moderate renal impairment, while no dosage adjustment is necessary for elderly patients without renal impairment

INDICATION AND ADMINISTRATION OF VARENICLINE (CHAMPIX®)

Varenicline is indicated for smoking cessation in adults. Smoking cessation therapies appear to be more likely to succeed in patients who are provided with addiction advice and support. The patients should set a date to stop smoking; varenicline dosing should start 1-2 weeks

before this date. Varenicline tablets should be swallowed whole with water and can be taken with or without food.

PHARMACOKINETIC OF NICOTINE

Nicotine addiction from cigarette smoking is a chemical, relapsing condition (Fiore et al 2000). Nicotine withdrawal is the presence of a characteristic withdrawal syndrome that develops after the abrupt cessation of, or reduction in, the use of nicotine – containing products following a prolonged period (at least several weeks) of daily use (American Psychiatric Association 2000). Nicotine withdrawal is characterized by at least 4 of the 8 symptoms that occur after abrupt smoking cessation or reduction in the amount of nicotine used (Table 2).

TABLE -2 Diagnostic Criteria for Nicotine Withdrawal

A. Daily use of nicotine for at least several weeks

B. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by four (or more) of the following

- (1) Dysphoric or decreased mood
- (2) Insomnia
- (3) Irritability, frustration or anger
- (4) Anxiety
- (5) Difficulty concentrating
- (6) Restlessness
- (7) Decreased heart rate
- (8) Increased appetite or weight gain

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder

Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by four (or more) of the following signs: dysphoric or decreased mood, insomnia, irritability, frustration or anger, anxiety, difficulty in concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

TABLE - 3 Varenicline: Administration in Daily Practice

A. Treatment period is 12 weeks

B. An additional course of 12 weeks of treatment may be considered for patients who have successfully quit at end of 12 weeks

C. Varenicline is supplied for oral administration in 2 strengths : 0.5 and 1.0 mg ; titration is as below

Days 1 – 3 : 0.5 mg once daily
Days 4 – 7 : 0.5 mg twice daily
Days 8 – End of treatment : 1 mg twice daily

D. Patients who cannot tolerate adverse effects may have dose lowered temporarily or permanently (0.5 mg BID)

HEALTH BENEFITS OF SMOKING CESSATION TREATED WITH VARENICLINE

Health benefits may begin soon after cessation and continue over a long term (US Dept. of Health and Human services 2004, American Cancer Society 2007). Two weeks up to Three months after cessation the lung function starts to improve, heart attack risk begins to drop, and circulating improves. One year after cessation, in regard with CHD, the excess risk is half that of a smoker. Five years after cessation, stroke risk returns to the level of a non-smoker. Ten years after cessation, lung cancer death rate is about half that of a smoker, and fifteen years after cessation, CHD risk is smaller to that of a non-smoker.

Mode of administration of varenicline (champix®) in daily practice can be easily understood as summarized in Table 3. Current drugs available worldwide, but not in Indonesia are Nicotine Replacement Therapy (NRT), comprising long acting NRT (Patch) and short acting NRT (Gum, Inhaler, Nasal Spray, Sublingual tablets or lozenges), and Anti Depressant, which consists of Bupropion SR and Nortriptyline (not approved for smoking cessation).

REFERENCES

American Cancer Society, 2007, *Guide to Quitting Smoking*. Retrieved March 16, from http://www.cancer.org/docroot/PED/content/PED_10_13X_Giude_for_Quiting_Smoking.asp.

American Psychiatric Association, 2000, *Diagnostic and Statistic Manual of Mental Disorders*, 4th edn, Text Revision (DSM-IV-TR) American Psychiatric Association, Arlington VA.

Cahill, K, Stead, L, Lancaster, T 2007, 'Nicotine receptor partial agonists for smoking cessation', *Cochrane Databased Syst Rev*, vol. 1, CD006103

Coe, JW, Brooks, PR, Vetelino, MG et al. 2005, 'Varenicline: an αlpha4ß2 nicotine receptor partials agonist for smoking cessation', *J Med Chem 48*, p. 3474.

Fiore, MC et al. 2000, *Clinical Practice Guideline. Treating Tobacco Use and Dependence*, Rockville, MD: US Department of Health and Human Service. Public Health Service, June

Jorenby, DE, Hays, JT, Rigotti, NA et al. 2006, 'Efficacy of varenicline, an α4ß2 nicotine acethylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial', *JAMA*, vol. 296, p. 56.

Kelly, AE 2002, 'Nicotine receptors: addictions smoking gun?', *Nat Med*, vol. 31, p. 447.

Rollema, H, Chambers, LK, Coe, JW et al. 2006, 'Pharmacological profile of the α4ß2 nicotine acethylcholine receptor partial agonist varenicline, an effective smoking cessation aid', *Neuropharmacology*, vol. 53, p. 985.

US Department of Health and Human Service, 2004, *The Health Consequences of Smoking: What It Means to You*, US Department of Health and Human Service, Center for Disease control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health

Williams, KE, Reeves, K, Billing, CB et al. 2007, 'A double blind study evaluating the long-term safety of varenicline for smoking cessation', *Curr Med Res Opin*, vol. 23, p. 793.

Wu, P, Wilson, K, Dimoulas, P, Mills, EJ 2006, 'Effectiveness of smoking cessation therapies: a systematic review and meta-analysis', *BMC Public Health* [E-pub ahead of print; Doi: 10.1186/1471-2458-6-300].