

# Smoking cessation in Asians: focus on varenicline

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**Abstract:** Smoking is a modifiable risk factor for morbidity and mortality caused by cancer, cardiovascular diseases, respiratory diseases, and many other diseases. Given the large population size and high prevalence of smoking in Asia, successful smoking cessation could potentially prevent the large number of premature deaths in Asians. However, most dependent smokers cannot successfully quit smoking due to nicotine addiction, and they need professional help and smoking cessation therapies. Varenicline is a highly selective partial agonist for the nicotinic acetylcholine receptor  $\alpha_4\beta_2$  subtype, which is believed to be responsible for mediating the reinforcing properties of nicotine. This article is a narrative review, which summarizes the smoking cessation efficacy, side effects, and cost utilities of varenicline in Asians. From this review, we conclude that varenicline is an effective medication that could assist smoking cessation in the Asian populations. The adverse events of varenicline are tolerable, and the most common events were nausea and abnormal dreams. Both the efficacy and tolerance of varenicline in Asians are similar to that in Western populations. Considering the cost utilities, varenicline should be recommended for use in smoking cessation and be covered by medical insurance in most Asian countries.

**Keywords:** effectiveness, safety, cost efficacy

## Introduction

Smoking is a modifiable risk factor for morbidity and mortality caused by cancer, cardiovascular diseases, respiratory diseases, and many other diseases. According to the World Health Organization, tobacco kills nearly six million people each year.<sup>1</sup>

The top ten biggest tobacco-consuming countries in the world include seven countries in Asia, with the People's Republic of China at number one and India at number two.<sup>2-7</sup> In 2010, there were an estimated 301 million current smokers in the People's Republic of China, with an estimated 28.1% of adult (52.9% of men and 2.4% of women) current smokers.<sup>2</sup> In India, the prevalence of smoking among men increased from 29.3% in 1998 to 36.4% in 2010, with 20.3% of women and 47.9% of men aged 15 and above smoking cigarettes or bidis.<sup>4</sup>

Given the large population size and high prevalence of smoking in Asia,<sup>2-7</sup> successful abstinence could potentially prevent the large number of premature deaths in this part of the world. Even when smokers are fully aware of the health hazards, most smokers intend to quit but cannot successfully quit smoking due to nicotine addiction.<sup>8</sup> Thus, nicotine-dependent smokers need professional assistance and smoking cessation treatment to quit successfully. Currently, smoking cessation treatments that can markedly increase long-term abstinence rates include pharmacotherapy, smoking cessation advice, and quitlines.<sup>9</sup> The 2008 US Guide to Quitting Smoking recommends that, except for groups with contraindications or for whom smoking cessation drugs have uncertain efficacy (eg, users of smokeless tobacco, light smokers, pregnant women, nursing women, and teenagers), clinicians should encourage all smokers intending to quit smoking to take smoking cessation medications combined with smoking cessation advice.<sup>9</sup>

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Varenicline is a highly selective partial agonist for the nicotinic acetylcholine receptor  $\alpha_4\beta_2$  subtype, which is believed to be responsible for mediating the reinforcing properties of nicotine. It has bidirectional adjustment effects of stimulation and antagonism. After combining with nicotinic acetylcholine receptors, varenicline works as an agonist, stimulating the release of dopamine in the brain, which can relieve nicotine withdrawal symptoms. Its antagonistic features can also prevent nicotine from combining with nicotinic acetylcholine receptors, thus reducing the satisfaction and reward of smoking.<sup>10</sup> It has been approved in over 100 countries worldwide, and involved in several smoking cessation guidelines as a first-line smoking cessation medication, including the China Smoking Cessation Guideline.<sup>9,11</sup> This article reviews the smoking cessation efficacy, adverse events (AEs), and cost utilities of varenicline in the Asian population.

## Methods

### Literature search strategies

This review is a narrative review, which entailed computer-based searches of Medline and the Cochrane Library to identify studies evaluating varenicline for tobacco cessation in Asians. The search covered June 2007 to July 2014, and included articles available online ahead of print publication. The search strings were “varenicline”, “smoking cessation”, “Asian”, “Chinese OR China or Taiwan”, “Japanese OR Japan”, “Korean OR Korea”, “Indian OR India”, “Philippines”, “Thailand”, “Vietnam”, and other Asian country names (though these obtained no related literature). Types of studies included meta-analysis, clinical randomized controlled trials, observational studies, and other related studies.

### Inclusion criteria

The studies were required to meet the following criteria: (i) the subjects should be Asians, (ii) the full original text should be accessible, and (iii) the contents of the study should include the relationship between varenicline and smoking cessation.

## Results

### Efficacy of smoking cessation in Asian populations

Clinical trials in Western populations indicated that varenicline could reduce the urge and desire to smoke, and satisfaction from smoking.<sup>12–14</sup> The results of the studies in Asians were roughly the same as those for Western populations.<sup>15,16</sup> In a 12-week, randomized, placebo-controlled, dose–response study, with a 40-week follow-up, mean scores in

Japanese smokers on the Minnesota Nicotine Withdrawal Scale (MNWS) Urge to Smoke subscale were significantly lower with varenicline 0.25, 0.5, 1 mg twice daily compared to placebo ( $P=0.01$ ,  $P<0.001$ , and  $P<0.001$ ), and indicated less negative affect ( $P=0.046$ ,  $P<0.001$ , and  $P<0.001$ ) and less restlessness ( $P=0.018$ ,  $P<0.001$ , and  $P<0.001$ ). Results for the mean Brief Questionnaire on Smoking Urges (QSU-Brief) scores suggested a similar effect of varenicline on the QSU-Brief total craving score to that observed by the MNWS.<sup>15</sup> Another trial conducted in Korea and Taiwan obtained similar results.<sup>16</sup>

The efficacy of varenicline as a smoking cessation aid has been reported in a number of studies.<sup>17–20</sup> A Cochrane meta-analysis indicated that the risk ratio of continuous abstinence rates (CARs) of smokers taking standard doses of varenicline for 6 months or longer was 2.27 times that of smokers taking placebo, and 1.52 times that of smokers taking bupropion sustained-release tablets.<sup>17</sup> Additionally, in studies where smokers taking varenicline could adjust the dosage schedule<sup>18</sup> or choose a flexible quit date approach,<sup>19</sup> the medication remained an effective smoking cessation aid. Prolonging treatment time with varenicline in smokers who were abstinent for the last week of treatment during the initial 12-week course increased the long-term smoking cessation rate and prevented relapse.<sup>20</sup> Studies have also found that smoking cessation efficacy of varenicline is better than bupropion or nicotine replacement therapy (NRT) at the end of the treatment period.<sup>12,13,21</sup>

Clinical studies on smoking cessation efficacy of varenicline in Asians indicate that varenicline can markedly increase the smoking cessation rate in this population.<sup>12,15,16,22,23</sup> In our primary clinical trial, which was a 24-week, randomized, double-blind, placebo-controlled trial of varenicline conducted in 333 subjects in the People's Republic of China, Singapore, and Thailand, 4-week continuous abstinence was achieved by 50.3% and 31.6% of participants in the varenicline and placebo groups, respectively ( $P=0.0003$ ). Continuous abstinence from weeks 9 to 24 was achieved by 38.2% and 25.0% of participants in the varenicline and placebo groups, respectively ( $P=0.0080$ ).<sup>22</sup> Comparable efficacy between Japanese and the US smokers has been reported in a study of 618 Japanese smokers. This study reported a complete abstinence rate of 65.4% for varenicline at weeks 9–12, which compared well to the 44% abstinence rate reported in the US studies.<sup>12</sup> Fagerström et al summarized and analyzed three placebo-controlled trials conducted in six Asian countries and found that 9–12-week CAR (58.6% vs 34.3%, odds ratio [OR] =2.74,  $P<0.0001$ ) and

9–24-week CAR (41.4% vs 25.3%, OR =2.08,  $P<0.0001$ ) for the varenicline group were both higher than for the placebo group.<sup>23</sup>

A double-blind, placebo-controlled, randomized trial in India found that varenicline was also effective for treating smokeless tobacco dependence. Although biochemically confirmed abstinence was greater for varenicline vs placebo (25.2% vs 19.5%), this was not statistically different (adjusted OR =1.6, 95% confidence interval [CI], 0.84–3.1,  $P=0.15$ ).<sup>24</sup> Further studies are required to confirm the effectiveness of varenicline in this specific population.

The results of an observational study on the efficacy of varenicline in Asians obtained similar findings as randomized trials. An observational study in adult Filipino smokers prescribed varenicline for the first time (during routine clinical practice) indicated that varenicline was efficacious as an aid for smoking cessation. At the end of week 12, 57.6% (95% CI, 52.0%–63.0%) of participants had been abstinent in the previous 7 days.<sup>25</sup> A smoking cessation program for outpatients, provided by a hospital in Southern Taiwan, found that varenicline use in a sample of treatment-seeking dependent smokers was associated with significantly higher abstinence rates than the nicotine patch.<sup>26</sup> A real-world observational study in a smoking cessation clinic in Taiwan, which involved 587 smokers followed up at 3 years, found that 36-month sustained abstinence rates showed a significant advantage for varenicline than for the nicotine patch (OR =7.94, 95% CI, 1.87–33.74).<sup>27</sup> A multicenter, prospective, non-comparative, observational study conducted in the People's Republic of China, India, Philippines, and Korea demonstrated an acceptable safety profile of varenicline, and the abstinence rates was consistent with those of randomized controlled trials. Overall, 46.4% (95% CI, 43.73%–49.07%) of subjects successfully quit smoking by the end of the treatment phase at week 12.<sup>28</sup> However, the compliance to medication use in the real world must be considered. An observational study conducted in a pulmonary clinic in South Korea found that although varenicline was effective in reducing the desire to smoke, compliance with medication was poor, and this needs to be overcome in clinical practice.<sup>29</sup>

## Safety and tolerance in Asian populations

Many studies have showed that the safety and tolerance of varenicline during clinical treatment are relatively good. The most common AEs reported are nausea and strange dreams.<sup>15,16,18,19</sup> The tolerability of varenicline in Asians is generally consistent with that of Western populations.<sup>22–28</sup> In our primary clinical trial, the most frequent categories of AEs were gastrointestinal disorders, psychiatric disorders, nervous

system disorders, general disorders, and administration site conditions, infections, and infestations. The most common AEs reported were nausea and strange dreams.<sup>22</sup> A clinical trial conducted among Chinese, Thai, and Singaporean smokers showed that the most commonly reported AEs in the varenicline group were nausea (29.1%), dizziness (14.5%), dry mouth (9.1%), and insomnia and drowsiness (both 6.1%).<sup>23</sup> The results of an observational study in adult Filipino smokers prescribed varenicline for the first time demonstrated that the most frequently reported AEs were headache (5.5%), dizziness (3.9%), and nausea (3.6%).<sup>25</sup>

Some post-marketing reports have drawn attention to neuropsychiatric AEs found in patients taking varenicline.<sup>30–32</sup> In February 2008, the US Food and Drug Administration announced that the psychiatric symptoms reported by patients who took varenicline include behavioral changes, agitation, sadness, suicidal thoughts, and suicide attempts or deaths. Prescribing information for varenicline was subsequently updated in the US, Europe, and the People's Republic of China to include warnings about neuropsychiatric events for doctors and patients. However, data from randomized, placebo-controlled studies, retrospective cohort studies, and a prospective cohort study of varenicline in patients without active mental disorders have not shown an increase in neuropsychiatric AEs.<sup>33–38</sup> Many randomized, double-blind, placebo-controlled studies have reported no evidence of exacerbation of symptoms in patients with mental disease, and varenicline was not associated with significantly higher smoking cessation rates vs placebo.<sup>39–42</sup> Within the Asian population, varenicline has not been reported to be associated with increasing psychiatric symptoms or suicide,<sup>22–29</sup> though further trials are needed to confirm this.

Three systematic reviews by Singh et al, Prochaska and Hilton, and Ware et al published between 2011 and 2013, have evaluated serious cardiovascular AEs with varenicline use.<sup>43–45</sup> Even though all three reviews demonstrated that serious cardiovascular AEs were nominally more frequent in varenicline-treated patients when compared to placebo, a significantly increased event rate was found only in the review by Singh et al.<sup>43</sup> The three reviews included similar trials but differed in the evaluation of outcomes and performance of summary statistic computation. In a clinical trial conducted in 85 Japanese smokers, the researchers evaluated the effect of varenicline-assisted smoking cessation on vascular endothelial function assessed by flow-mediated vasodilation (FMD). Participants were evaluated by FMD prior to, and 3 months after, complete smoking cessation. The researchers found that FMD was significantly increased from

4.0%±1.8% to 5.5%±2.2% ( $P<0.01$ ,  $n=22$ ) 3 months after complete cessation. FMD also increased during varenicline use (from 3.7%±2.7% to 4.3%±2.8%,  $n=11$ ). The observations suggest that in ceasing smokers, varenicline and smoking cessation do not lead to worsening of the vascular endothelial function.<sup>46</sup> Within the Asian population, there have been no reports of varenicline being associated with increasing serious cardiovascular AEs,<sup>22–29</sup> though further trials are needed to confirm this.

## Cost efficacy of varenicline

Since in most Asian countries, smokers would purchase varenicline themselves, the cost utility of varenicline must be evaluated. A cost-utility analysis of two 12-week smoking cessation interventions in Japan (smoking cessation counseling by a physician vs varenicline in addition to counseling) analyzed lifetime medical costs and quality-adjusted life-years (QALYs) from the perspective of the health care payer. It was found that varenicline would save Japanese yen 43,846 (\$US 381; \$US 1 = yen 115; October 2007) in direct medical costs and generate an increase of 0.094 QALYs in male smokers. In females, the incremental cost-effectiveness ratio was yen 346,143 per QALY gained. Varenicline was estimated to save yen 23.7 billion (\$US 206 million) of the medical costs for tobacco-associated diseases for the whole population. Overall savings were reported to be yen 9.5 billion. This study concluded that varenicline appears to be cost-effective and may contribute to future medical cost savings in Japan.<sup>47</sup>

Another similar study conducted in South Korea evaluated the cost-effectiveness of varenicline compared to other smoking cessation interventions, bupropion, NRT, and willpower. The incremental cost-effectiveness ratio for varenicline vs NRT was reported to be \$US 4,809 per QALY over a lifetime.<sup>48</sup>

However, studies conducted in Vietnam found that varenicline did not fall within the range of being “cost-effective” under different scenarios. They revealed that prices of pharmaceuticals must be substantially lower than the levels from other countries if pharmacological therapies are to be cost-effective in Vietnam.<sup>49</sup>

## Discussion

Meta-analyses indicate that varenicline is more effective than bupropion and single-form NRT for smoking cessation. Pooled analysis and many placebo-controlled, randomized trials and real-world studies also strongly suggest that varenicline is an effective drug that assists in smoking cessation

in Asians. Moreover, varenicline was recommended in the China Smoking Cessation Guideline as a first-line smoking cessation medication in 2007.<sup>11</sup>

The safety and tolerance of varenicline during clinical use are relatively good, and the most common AEs in clinical trials were nausea and abnormal dreams, which are similar to the AEs reported in the Western population. Although several clinical case reports suggested that varenicline might be associated with neuropsychiatric events or serious cardiovascular events, there is no evidence that varenicline was associated with a higher rate of, or an exacerbation of, mental diseases, or increasing serious cardiovascular AEs in Asians. Further trials are needed to confirm these reports.

Half of the current Asian smokers, most of whom are young men at present, will die prematurely due to smoking-related diseases in the next few decades. Given its high cost efficacy and safety profile, varenicline should be recommended for use in smoking cessation, and be covered by medical insurance in most Asian countries.

## Disclosure

Chen Wang and Dan Xiao have consulted for a number of companies with an interest in clinical trials of medication and medical professionals training for tobacco dependence treatments, including Pfizer Inc., and they have been investigators for Pfizer-sponsored clinical trials. Shuilian Chu reports no conflicts of interest in this work.

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