Effectiveness and safety of varenicline as an aid to smoking cessation: results of an inter-Asian observational study in real-world clinical practice

C. Wang, B. Cho, D. Xiao, D. Wajsbrot, P. W. Park

SUMMARY

Aims: To evaluate the effectiveness and safety of varenicline for smoking cessation among Asian adult smokers in real-world clinical practice. Methods: A multicentre, prospective, non-comparative, observational study conducted in China, India, Philippines and Korea. Adult smokers, willing to make a quit attempt, who reached a joint decision with the investigators to take varenicline received 1 mg twice daily (after 1-week titration) for 12 weeks. No exclusion criteria were specified. Effectiveness evaluations included smoking abstinence status for the 7-day period before the Week 12 visit and the last observed study visit, determined by verbal reporting using a nicotine use inventory and carbon monoxide levels if part of usual practice (end of study only). The safety profile of varenicline was also assessed. Results: Of 1377 subjects enrolled in the study, 1373 (99.7%) received varenicline and were evaluated for safety and effectiveness. Overall, 46.4% [95% confidence interval (CI): 43.73–49.07] of subjects successfully quit smoking by the end of the treatment phase at Week 12. When analysed by country, 57.1% (95% CI: 53.55–60.65) of subjects from China, 52.8% (95% CI: 45.21–60.25) of subjects from India, 51.0% (95% CI: 36.60–65.25) of subjects from Philippines and 20.3% (95% CI: 16.29–24.73) of subjects from Korea had quit smoking at Week 12. The most commonly reported treatment-related adverse event was nausea (11.5%). Conclusions: This study demonstrates the effectiveness and acceptable safety profile of varenicline for smoking cessation in a real-world setting among Asian populations, with results consistent with those of varenicline randomised controlled trials.

Introduction

Smoking is a modifiable risk factor for morbidity and mortality caused by cancer, cardiovascular disease and respiratory disease. According to the World Health Organization, more than 5.4 million people worldwide die each year of smoking-related diseases (1).

Asia has the largest population and the largest smoking population in the world (2–9). In 2010, there were an estimated 301 million current smokers in China, making this country the largest consumer of tobacco in the world, with an estimated 28.1% of adults (52.9% of men and 2.4% of women) current smokers (2). In India, the prevalence of smoking among men increased from 29.3% in 1998 to 32.7% in 2005 (5), with 1.4% of women and 32.7% of men aged 15–49 years smoking cigarettes or bidis (also known as beedies) in 2005 (4). The Global Youth Tobacco Survey (GYTS), conducted among school-going children aged 13–15 years in northern India, reported ever-use tobacco prevalence of 2.9–8.5% in boys and 1.5–9.8% in girls, although the majority reported a desire to quit (3).

In recent years, a growing number of Asian countries have begun to attach importance to tobacco control, and there has been great progress. For example, the prevalence of smoking in men aged ≥ 20 years in South Korea declined from 73.2% in 1992 to 52.2% in 2006 (6). Similarly, the prevalence of smoking among the general population of Japan has also declined in recent years: from 2000 to 2008, smoking prevalence among Japanese men and women declined from 53.5% to 39.5% and from 13.7% to 12.9% respectively (7). In Singapore, the prevalence of regular smoking decreased from 28.6% in 1987 to 20.7% in 1993 (8).
In Thailand, male smoking prevalence was close to 60% in 1991, but policies implemented between 1991 and 2006 have decreased smoking prevalence by 25% compared with predicted figures in the absence of the policies (9).

Given the large population size and high prevalence of smoking in Asia (2,10,11), successful smoking cessation therapies would potentially lead to the prevention of many premature deaths in this part of the world. Varenicline is a highly selective partial agonist for the nicotinic acetylcholine receptor α4β2 subtype, which is believed to be responsible for mediating the reinforcing properties of nicotine. It is thought to act as both a partial agonist to relieve nicotine craving and withdrawal, and an antagonist to reduce the psychogenic reward associated with smoking.

Varenicline was approved for adults over the age of 18 as an aid to smoking cessation treatment in the United States and Europe in 2006 and in countries in the Asia Pacific region in 2007. In randomised, placebo-controlled clinical trials among Asian populations, varenicline significantly improved smoking abstinence vs. placebo, and adverse events (AEs) were predominantly of mild or moderate intensity (10–13). In addition, varenicline has demonstrated greater efficacy in randomised clinical trials compared with other smoking cessation pharmacotherapies (14–18). Furthermore, to evaluate whether the clinical efficacy of varenicline as demonstrated in the randomised clinical trials (10–18) would also be observed in usual care settings in the community, the clinical effectiveness of varenicline has been recorded in real-world observational studies conducted in clinical practice settings across Europe (19,20) and in the Philippines (21). Clinical effectiveness studies assess whether or not an intervention is beneficial when provided under usual circumstances of healthcare practice (22). In addition to the demonstrated efficacy in clinical trials and effectiveness in real-world settings of varenicline as an aid to smoking cessation, it is also predicted that using varenicline for smoking cessation would save direct medical costs and generate an increase in quality-adjusted life years, as well as reduce the high risk of morbidity and mortality associated with continued smoking (23,24). The purpose of this study was to assess the effectiveness and safety of varenicline for smoking cessation in Asian subjects in an observational study in real-world clinical practice.

Methods

Study design & participants
A 12-week, prospective, non-comparative, observational study was conducted at 110 sites across four Asian countries (China, India, Philippines, Korea) between February 2009 and July 2010. Adults who were regular cigarette smokers (there was no minimum or maximum limit on the number of cigarettes smoked per day), willing to make an attempt to quit smoking, and who met the prescribing criteria for varenicline as per the local Prescribing Information (PI), were enrolled in the study. There were no exclusion criteria specified for the study, as it was a real-world observational study, as long as participants met the local prescribing criteria.

The final study protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the investigational centres participating in the study, as required, prior to the enrolment of any participants.

At study enrolment, nicotine dependence was assessed using the Fagerström Test of Nicotine Dependence (FTND) (25). Participants were informed of the benefits of counselling and how to receive it within the clinical environment. Participants agreed to a quit date and started treatment up to 2 weeks prior to the quit date. Investigators and participants reached a joint decision to use varenicline and investigators discussed varenicline product information with participants as per usual practice. Once the decision to take varenicline had been reached, participants were informed to take varenicline for 12 weeks, in accordance with the local varenicline PI: varenicline 0.5 mg once daily for the first 3 days, titrated to 0.5 mg twice daily on Days 4–7, then 1 mg twice daily from Day 8 to the end of the 12-week treatment phase. There were no restrictions on the use of concomitant medications apart from those specified in the local varenicline PI. A schematic diagram of the study design is shown in Figure 1.

Participants had clinic visits only at study enrolment and end of study (Week 12). Between Weeks 1 and 11, consultation only took place if this were part of normal practice for smoking cessation attempts at the clinic.

Prior and concomitant medications and comorbidities
There were no restrictions on prior and concomitant medications or comorbidities apart from the usual prescribing information in each country.

Effectiveness evaluations
Effectiveness endpoints included smoking abstinence (i.e. not a single puff) status for the 7-day period before the Week 12 visit; smoking abstinence status for the 7-day period before the last observed study...
visit; smoking abstinence status at Week \( t (t = 3–11) \), which was defined as the last known abstinence status during the previous 4 weeks; carbon monoxide (CO) level at the last observed study visit; average number of cigarettes smoked at Week 12; and the last observed study visit.

**Clinical evaluations**

Smoking abstinence status was assessed using the nicotine use inventory (NUI). The NUI consisted of the following three questions: (i) ‘Has the subject smoked any cigarettes (even a puff) in the last 7 days?’; (ii) ‘Has the subject used any other tobacco products (e.g. pipe, cigars, chew, snuff) in the last 7 days?’; and (iii) ‘What is the average number of cigarettes smoked per day over the last 7 days?’ Abstinence status was also assessed using CO levels, if part of usual practice, at baseline and end of study only. A positive CO level was defined as > 10 ppm. Participants were deemed to have quit if they responded negatively to all four criteria. If one of the criteria was missing, it was not used to determine smoking status. If all four criteria were missing, subjects were given a smoking status of ‘unknown’ and considered smokers for the analysis.

**Safety evaluations**

Adverse events were reported descriptively using Medical Dictionary for Regulatory Activities (MedDRA) coding. Safety data were collected and assessed using standard methods from smoking cessation trials.

**Other evaluations**

Other evaluations included dose and duration of prescribed varenicline and average daily dose for Days 1–3, 4–7 and 8 to end of treatment; healthcare utilisation, including reimbursement type (e.g. insurance or self-funded); and employment status.

**Statistical analysis**

The primary analysis population was the full analysis set (FAS) which included all participants who received \( \geq 1 \) dose of study medication. All effectiveness analyses were performed using the FAS except for smoking abstinence at Week \( t \), which was performed using the observed cases (OC) population (those participants in the FAS with observed, not missing values). Analysis methods were descriptive; no formal statistical testing was performed. For categorical variables, count and percentage for each category were presented along with two-sided 95% confidence intervals (CIs) for proportions (calculated using the Clopper–Pearson method).

The study planned to enrol approximately 2500–3000 subjects; however, only 1377 subjects were enrolled within the prespecified, preplanned recruitment period for the study. Thus, although fewer subjects than anticipated were enrolled by the prespecified end of recruitment date, the study ended on that date as planned. Although fewer than originally planned, this number of subjects was sufficient to determine success rates nominally to within ±2.6% with 95% confidence and was considered adequate to draw conclusions from the data.

**Results**

**Subject disposition and baseline characteristics**

Overall, 1377 subjects were enrolled in the study, and of these, 1373 (99.7%) received study medication and were evaluated for safety and effectiveness (Figure 2). Four subjects did not receive treatment: one was no longer willing to participate, one died, and no reason was provided for the other two subjects.

The majority of the subjects were male subject (93.2%) and were age 18–44 years (50.8%) (Table 1). Overall, the median number of years participants had smoked was 20 years, the median number of cigarettes per day was 20 and the mean FTND score was 5.5 (Table 1). Furthermore, most participants had not made any serious quit attempts in the past year (Table 1).

**Prior and concomitant comorbidities and treatments**

The most common medications used prior to the start of the study were acetylsalicylic acid [99/1373 (7.2%)], atorvastatin [44/1373 (3.2%)] and metformin [29/1373 (2.1%)]. Overall, 546/1373 (39.8%) subjects used concomitant drug treatments during the study; the most commonly used were acetylsalicylic acid [110/1373 (8.0%)], atorvastatin [54/1373 (3.9%)] and metformin [32/1373 (2.3%)]. Of 701 subjects with non-missing data on previous non-drug.
treatment for primary diagnosis, 661 (94.3%) received smoking cessation counselling and 190 (27.1%) attended a quit smoking clinic.

Compliance and duration of treatment exposure
A total of 340 (24.8%) subjects discontinued from the study (China, 0.8%; India, 20.0%; Philippines, 45.1%; Korea, 74.3%) (Figure 2). The median (range) duration of treatment was 43.0 (1–271) days, with 494/1353 subjects (36.0%) taking varenicline for 61–90 days.

Effectiveness evaluations
Overall, the proportion of subjects with an abstinence status of ‘Quit’ at Week 12 was 46.4% (95% CI: 43.73–49.07) (Figure 3A). When analysed by country, 441 of 772 subjects (57.1%; 95% CI: 53.55–60.65) from China, 95 of 180 subjects (52.8%; 95% CI: 45.21–60.25) from India, 26 of 51 subjects (51.0%; 95% CI: 36.60–65.25) from Philippines and 75 of 370 subjects (20.3%; 95% CI: 16.29–24.73) from Korea had a status of ‘Quit’ at Week 12.

At the last observed study visit, the overall proportion of subjects with a status of ‘Quit’ was 50.3% (95% CI: 47.58–52.93) (Figure 3B). When analysed by country, 441 of 772 subjects (57.1%; 95% CI: 53.55–60.65) from China, 103 of 180 subjects (57.2%; 95% CI: 49.65–64.55) from India, 30 of 51 subjects (58.8%; 95% CI: 44.17–72.42) from Philippines and 116 of 370 subjects (31.4%; 95% CI: 26.66–36.35) from Korea had a status of ‘Quit’ at the last observed study visit.
Between Weeks 3 and 11, routine clinic visits/contact took place only if this was normal practice for smoking cessation attempts at the clinic. Overall, 31.3% of subjects who provided data on routine visits at Week 3 had an abstinence status of ‘Quit’. At Week 11, 59.2% of subjects had a status of ‘Quit’ (Table 2).

At baseline, median (range) CO levels for 361 subjects with available data (CO measures were not mandatory) were 14.0 (2.0–40.0) ppm vs. 3.0 (0–22.0) ppm at the last observed study visit for 115 subjects with non-missing data. The median (range) of cigarettes smoked per day for 1256 subjects with non-missing data at baseline was 20.0 (1.0–80.0) and 10.0 (1.0–80.0) for 518 subjects with non-missing data at the last observed study visit.

Safety evaluations

Of the 1373 subjects who received varenicline, 386 (28.1%) experienced an all-causality AE and 315 (22.9%) experienced an AE that was considered to be treatment-related (Table 3). The most frequently reported (≥2.0% of participants) all-causality and treatment-related AEs were nausea (11.5 and 11.1% respectively), dizziness (3.1 and 2.9% respectively), insomnia (3.0 and 2.3% respectively) and abnormal dreams (both 2.0%). The majority (440/585 events; 75.2%) of all-causality AEs were mild in severity.

Eleven (0.8%) subjects experienced an all-causality serious AE (SAE) and two subjects (0.1%) experienced SAEs that were considered to be treatment-related (one participant: nausea; one participant: nausea and dizziness). One subject died prior to receiving treatment (aortic aneurysm rupture) and one subject died during the study (severe acute respiratory failure and severe chronic obstructive pulmonary disease). Both AEs were considered to be unrelated to varenicline treatment.
## Other evaluations

### Treatment

Overall, the median daily dose of varenicline for Days 1–3 was 0.5 mg; for Days 4–7 was 1.0 mg; and for Days 8 through the end of treatment was 2.0 mg. Varenicline treatment was self-funded for 99.2% of subjects (China: 99.5%; India: 98.3%; Philippines: 94.1%; Korea: 100%).

### Baseline characteristics

Most subjects were employed full time [overall: 80.3% (China: 82.2%; India: 80.6%; Philippines: 56.5%; Korea: 78.6%)]. Possession of public health insurance varied between countries. The majority of subjects had public health insurance in China (75.4%) and Korea (98.0%); however, the majority had no health insurance in India (72.9%) and Philippines (68.6%).

## Discussion

This was an observational study evaluating the effectiveness and safety of varenicline in a real-world smoking cessation practice setting in four Asian countries: China, India, Philippines and Korea. At the end of treatment (12 weeks), an overall 7-day point prevalence of abstinence rate of 46.4% (95% CI: 43.7--49.0) was observed.

After 12 weeks of varenicline treatment, the overall abstinence rate (46.4%) and the abstinence rates of three of the four participating countries [China, 57.1%; India, 52.8% and Philippines, 51.0%] were similar to abstinence rates reported in varenicline randomised controlled trials: 44% (14), 43.9% (15), 40.8% (16) and 49.4% (26). However, abstinence after 12 weeks of varenicline treatment in

### Table 2 Smoking abstinence status in each 7-day period between Weeks 3 and 11, observed cases

| Visit     | Varenicline (N = 1373) n (%) |
|-----------|------------------------------|
| Week 3    |                              |
| n         | 667                          |
| Smoking   | 465 (68.7)                   |
| Quit      | 212 (31.3)                   |
| Week 4    |                              |
| n         | 799                          |
| Smoking   | 494 (61.8)                   |
| Quit      | 305 (38.2)                   |
| Week 5    |                              |
| n         | 988                          |
| Smoking   | 539 (54.6)                   |
| Quit      | 449 (45.4)                   |
| Week 6    |                              |
| n         | 959                          |
| Smoking   | 501 (52.2)                   |
| Quit      | 458 (47.8)                   |
| Week 7    |                              |
| n         | 888                          |
| Smoking   | 448 (50.5)                   |
| Quit      | 440 (49.5)                   |
| Week 8    |                              |
| n         | 812                          |
| Smoking   | 393 (48.4)                   |
| Quit      | 419 (51.6)                   |
| Week 9    |                              |
| n         | 765                          |
| Smoking   | 343 (44.8)                   |
| Quit      | 422 (55.2)                   |
| Week 10   |                              |
| n         | 702                          |
| Smoking   | 313 (44.6)                   |
| Quit      | 389 (55.4)                   |
| Week 11   |                              |
| n         | 605                          |
| Smoking   | 247 (40.8)                   |
| Quit      | 358 (59.2)                   |

### Table 3 Incidence of all-causality and treatment-related adverse events

| Varenicline, n (%) | All-causality | Treatment-related |
|--------------------|--------------|------------------|
| Subjects with AEs  | 386 (28.1)   | 315 (22.9)       |
| Subjects with serious AEs | 11 (0.8) | 2 (0.1) |
| Discontinuation caused by AE | 93 (6.8) | 83 (6.0) |
| Dose reduction or temporary discontinuation caused by AE | 66 (4.8) | 58 (4.2) |

Incidence of AEs reported by > 1% of study subjects

|                             | All-causality | Treatment-related |
|-----------------------------|--------------|------------------|
| Nausea                      | 158 (11.5)   | 153 (11.1)       |
| Dizziness                   | 43 (3.1)     | 40 (2.9)         |
| Insomnia                    | 41 (3.0)     | 32 (2.3)         |
| Abnormal dreams             | 28 (2.0)     | 28 (2.0)         |
| Headache                    | 20 (1.5)     | 14 (1.0)         |
| Weight increased            | 17 (1.2)     | 15 (1.1)         |

Incidence of psychiatric disorders reported by ≥ 0.2% of study subjects

|                             | All-causality | Treatment-related |
|-----------------------------|--------------|------------------|
| Insomnia                    | 41 (3.0)     | 32 (2.3)         |
| Abnormal dreams             | 28 (2.0)     | 28 (2.0)         |
| Anxiety                     | 7 (0.5)      | 4 (0.3)          |
| Restlessness                | 7 (0.5)      | 4 (0.3)          |
| Sleep disorder              | 5 (0.4)      | 3 (0.2)          |
| Bradyprenia                 | 4 (0.3)      | 4 (0.3)          |
| Depression                  | 4 (0.3)      | 4 (0.3)          |

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 13.1). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 13.1). AE, adverse event.
Korea (20.3%) was noticeably lower than the other Asian countries in this study.

The lower rate of abstinence in Korea may be attributable to several differences between the way the trial was conducted and data were recorded compared with the other countries. (i) A higher percentage of subjects in Korea had a smoking status of ‘unknown’, which in turn could have been attributable to the high incidence of discontinuations. (ii) Differences in reporting criteria: in China, India and Philippines, a participant with dosing interruptions or who discontinued study treatment, but attended the Week 12 study visit, was considered to have completed the study. In contrast, in Korea, similar participants were recorded as having discontinued from the study. (iii) Differences in reimbursement policies: in Korea, the cost of varenicline is high compared with other drugs, as it is not reimbursed by the Korean National Insurance System. In addition, consultation fees at smoking clinics are not reimbursed by the Korean National Insurance System, which may deter those smokers from completing the treatment regardless of initial quitting success or failure. (iv) Differences in enrolment criteria: in Korea, many participants who were not ready to quit smoking may have been enrolled in the study. Some doctors may have persuaded these subjects to try varenicline as an aid to smoking cessation, as it has been shown to increase quit attempts in smokers who are not currently trying to quit (27).

The AEs most commonly reported by participants in this observational study were similar to those recorded in randomised clinical trials of varenicline – nausea, dizziness, insomnia and abnormal dreams (11–16,28,29) – and led to a small number of discontinuations (6.8%). However, the incidence of the AEs in this observational study was much lower than in randomised clinical trials of varenicline: nausea was reported by 11.5% of patients vs. > 30% in most randomised clinical trials; insomnia in 3.0% vs. > 14% in randomised clinical trials; and abnormal dreams in 2.0% vs. > 10% in randomised clinical trials. As AEs were collected in a manner consistent with previous randomised clinical trials of varenicline, this discrepancy may be attributable to the lower frequency of contacts, and therefore opportunities to observe/report AEs, in routine smoking cessation clinics compared with the weekly follow-up visits in RCTs.

There are a number of limitations to this study. (i) As a multicountry observational study, the data provides valuable insights into the effectiveness and safety of varenicline in routine clinical practice. However, as in any observational study, procedures and clinical follow-up were not standardised and may have differed between participating countries based on local clinical practice. Therefore, findings may be different in other populations or settings. (ii) As participants were not followed beyond Week 12, relapse rates following the 12-week treatment phase were not evaluated in this study. (iii) The comparisons between countries is a posthoc analysis that is exploratory in nature and therefore not powered to determine differences between subgroups. (iv) There is no control group in this observational trial, as there would be in a randomised, controlled clinical trial because placebo would not be prescribed in routine clinical practice; therefore any potential ‘placebo effect’ cannot be addressed, i.e. do some subjects quit smoking just because they are being cared for by a doctor? (v) This study measured effectiveness in real-world clinical practice settings and not efficacy as assessed in randomised clinical trials; thus, CO levels were collected only if they were part of the usual routine. It is notable that CO level data were available for 26% (361/1373) of subjects at baseline and 8% (115/1373) of subjects at last observed study visit. (vi) Treatment response was obtained at a single visit, not continuously. Randomised clinical trials of varenicline use more conservative primary endpoints, e.g. 4-week continuous abstinence rate; whereas this effectiveness trial used 7-day point prevalence instead.

Conclusions

This study has demonstrated the effectiveness and acceptable safety profile of varenicline for smoking cessation in a real-world clinical practice setting among Asian populations. The safety profile of varenicline in this real-world observational study was consistent with previous reports (11–16,25,26), and the overall abstinence rate of 46.4% at the end of treatment was consistent with results from published varenicline randomised clinical trials (11–13,15–17,28,29).

Author contributions

PWP contributed to the study design, analysis and manuscript preparation and approval. CW and DX contributed to the concept, data interpretation, drafting article, data collection, critical revision of article and approval of article. BC contributed to the concept, data interpretation, drafting article, data collection, critical revision of article and approval of article. DW provided statistical support to the study, including data analysis and interpretation, and contributed to the preparation of the manuscript.
Acknowledgements

This study was designed, conducted and funded by Pfizer Inc. All authors contributed to the data analysis and manuscript preparation. Editorial support for this manuscript was provided by Alexandra Bound, PhD and Michelle Jenvey, PhD of UBC Scientific Solutions and was funded by Pfizer.

References

1 WHO. WHO report on the global tobacco epidemic, 2008: the MPOWER package/World Health Organization. Geneva: World Health Organization, 2008.
2 Li Q, Hsia J, Yang G. Prevalence of smoking in China in 2010. N Engl J Med 2011; 364: 2469–70.
3 Banerjee A. Tobacco use patterns among military recruits. Med J Armed Force India 2000; 56: 192–4.
4 International Institute for Population Sciences (IIPS). National Family Health Survey (NFHS-3) 2005–06: India: Volume I. 2007. http://pdf.usaid.gov/pdf_docs/PNADK385.pdf (accessed January 2012).
5 International Institute for Population Sciences (IIPS). National Family Health Survey (NFHS-3), 2005–06: India: Volume II. 2007. http://www.measuredhs.com/pubs/pdf/frind3/frind3-vol2.pdf (accessed January 2012).
6 Korean Ministry of Health and Welfare. Smoking Survey 1988–2007 [in Korean]. Korean Ministry of Health and Welfare: Seoul, 2007.
7 Japan Tobacco Inc. Nationwide Cigarette Smoking Survey [in Japanese]. 2008. http://www.health-net.or.jp/tobacco/product/pd090000.html (accessed January 2012).
8 Lim MK, Soh CS, Tan YS, Leong CK. Smoking in the Singapore Armed Forces. Singapore Med J 1997; 38: 50–3.
9 Levy DT, Benjakut K, Ross H, Rithiphabkdee B. The role of tobacco control policies in reducing smoking and deaths in a middle income nation: results from the Thailand SimSmoke simulation model. Tob Control 2008; 17: 53–9.
10 Fagerström K, Nakamura M, Cho HJ et al. Varenicline treatment for smoking cessation in Asian populations: a pooled analysis of placebo-controlled trials conducted in six Asian countries. Curr Med Res Opin 2010; 26: 2165–73.
11 Nakamura M, Oshima A, Fujimoto Y et al. Efficacy and tolerability of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. Clin Ther 2007; 29: 1040–56.
12 Tsai ST, Cho HJ, Cheng HS et al. A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. Clin Ther 2007; 29: 1027–39.
13 Wang C, Xiao D, Chan KP et al. Varenicline for smoking cessation: a placebo-controlled, randomized study. Respiratory 2009; 14: 384–92.
14 Gonzalez D, Rennard SI, Nides M et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 47–55.
15 Jorenby DE, Hays JT, Rigotti NA et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 56–63.
16 Nides M, Oncken C, Gonzales D et al. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Arch Intern Med 2006; 166: 1561–8.
17 Aubin HJ, Bobak A, Britton JR et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008; 63: 717–24.
18 Stapleton JA, Watson L, Spirling LI et al. Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those with mental illness. Addiction 2008; 103: 146–54.
19 Boudrez H, Gratziou C, Messig M, Metcalfe M. Effectiveness of varenicline as an aid to smoking cessation: results of an inter-European observational study. Curr Med Res Opin 2011; 27: 769–75.
20 Andreas S, Chemot J-F, Diebold R, Peachey S, Mann KF. Effectiveness of varenicline as an aid to smoking cessation in primary care: an observational study. Eur Addict Res 2013; 19: 47–54.
21 Park PW, Casiano EM, Escoto L, Claverys AM. Observational study of safety and efficacy of varenicline for smoking cessation among Filipino smokers. Curr Med Res Opin 2011; 27: 1869–75.
22 Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. BMJ 1999; 319: 652–3.
23 Igarashi A, Takuma H, Fukuda T, Tsutani K. Cost-utility analysis of varenicline, an oral smoking-cessation drug, in Japan. PharmacoEconomics 2009; 27: 247–61.
24 Bae JY, Kim CH, Lee EK. Evaluation of cost-utility of varenicline compared with existing smoking cessation therapies in South Korea. Value Health 2009; 12 (Suppl. 3): S70–3.
25 Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991; 86: 1119–27.
26 Oncken C, Gonzales D, Nides M et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med 2006; 166: 1571–7.
27 Hughes JR, Rennard SI, Fingar JR et al. Efficacy of varenicline to prompt quit attempts in smokers not currently trying to quit: a randomized placebo-controlled trial. Nicotine Tob Res 2011; 13: 955–64.
28 Tashkin DP, Rennard S, Hays JT et al. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest 2011; 139: 591–9.
29 Bolliger CT, Isa S, Posadas-Valay R et al. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. Clin Ther 2011; 33: 465–77.

Paper received July 2012, accepted December 2012

© 2013 Blackwell Publishing Ltd

Int J Clin Pract, May 2013, 67, 5, 469–476