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SPEAKER SERIES

Goodfellow Symposium 2018:

Supporting smoking cessation in chronic obstructive pulmonary disease

Making Education Easy 2018

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Medical specialist

Dr Stephen Child is a Canadian-trained General Physician who immigrated to New Zealand in 1991. He worked in Dargaville for 2½ years before moving to his current role as General Physician at Auckland District Health Board (ADHB) in 1994. From 1994-2018 he was the Director of Clinical Training at ADHB before he assumed his new position as Chief Medical Officer of Southern Cross Health Society. Clinically, he has an interest in asthma and general internal medicine with a strong passion for medical education.

Dr Child has given numerous talks on topics of general medicine, asthma and medical education. He has authored or co-authored more than 50 articles on medical workforce / medical education and has a passion for our trustworthiness and the future of medicine and is a current Member of the Clinical Governance Group for ProCare and Homecare Medical and past Chair of the New Zealand Medical Association.

He continues weekly private clinics specialising in medicine / respiratory diseases and is a full consultant within the Department of General Medicine at ADHB.

The 2018 Goodfellow Symposium was held in Auckland in March 2018. Dr Stephen Child, medical specialist from ADHB, discussed smoking cessation in chronic obstructive pulmonary disease (COPD) at a breakfast session sponsored by Pfizer. COPD is the fourth leading cause of death in New Zealand, after ischaemic heart disease, stroke and lung cancer. Smoking is the most important risk factor for COPD and according to recent data, 15.7% of adults in New Zealand were current smokers in 2016/2017.[1] This session focused on smoking cessation intervention in patients with COPD, the role of counselling and support and provided an overview of treatment options for nicotine dependence. The session discussed recent data including the first randomised, placebo-controlled trial of varenicline in patients with mild-to-moderate COPD, and the EAGLES study, which evaluated the neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders.

Smoking: an important risk factor for COPD

There is a plethora of inhaled therapies for COPD available in New Zealand. Generally, these medications aim to help manage symptoms and reduce exacerbations of COPD. Non-pharmacological therapies for treating symptoms include rehabilitation, exercise, nutrition and self-management – all have been shown to improve the symptoms of COPD and mildly reduce exacerbations. There are only two interventions that have definitely been shown to improve prognosis in COPD – oxygen therapy in severe hypoxic COPD[2,3] and smoking cessation.[4]

A key feature of COPD is an accelerated rate of decline in forced expiratory volume in 1 second (FEV_1). The ECLIPSE study analysed changes in FEV_1 (after administration of a bronchodilator) over a 3-year period in 2163 patients with COPD.[5] Over the study period, 38% of patients had a decline in FEV_1 of more than 40 mL per year, 31% had a decline of 21 to 40 mL per year, 23% had a change that ranged from a decrease of 20 mL per year to an increase of 20 mL per year, and 8% had an increase of more than 20 mL per year. This shows that the rate of change in FEV_1 among patients with COPD is highly variable and that we are still not sure what the natural history is of change in FEV_1 over time. Although COPD is considered to be a progressive disease, only 38% of patients in the ECLIPSE study had a rate of decline in FEV_1 of more than 40 mL per year, while more than half the patients had a rate of decline in FEV_1 no greater than that which has been observed in people without lung disease. Current smoking was most strongly associated with the rate of decline in FEV_1, which suggests that smoking cessation is an important tool in prevention for patients at all stages of COPD.

Smoking cessation in New Zealand

The societal cost of smoking in New Zealand is estimated at $1.685 billion or about 1% of GDP per annum.[6] Tobacco is the leading cause of preventable morbidity and mortality in this country, accounting for an estimated 5000 deaths per year.[6] According to the 2009 New Zealand Tobacco Use Survey, four out of five smokers would not smoke if they had their life over again.[7] Three in five smokers tried to quit in the last 5 years and approximately 40% of smokers attempted to quit in the last year.[7]

Counselling

Options for smoking cessation in New Zealand include individual counselling by GPs, group counselling, proactive telephone counselling (Quitline), and web and text-based support. Regarding individual counselling, one of the best actions GPs can take is to follow the New Zealand Guidelines for Helping People to Stop Smoking - the ABC pathway:[8]

- **Ask** about and document every person's smoking status.
- Give **Brief advice** to stop to every person who smokes.
- Strongly encourage every person who smokes to use **Cessation support** (a combination of behavioural support and stop-smoking medicine works best) and offer to help them access it. Refer to, or provide, cessation support to everyone who accepts your offer.

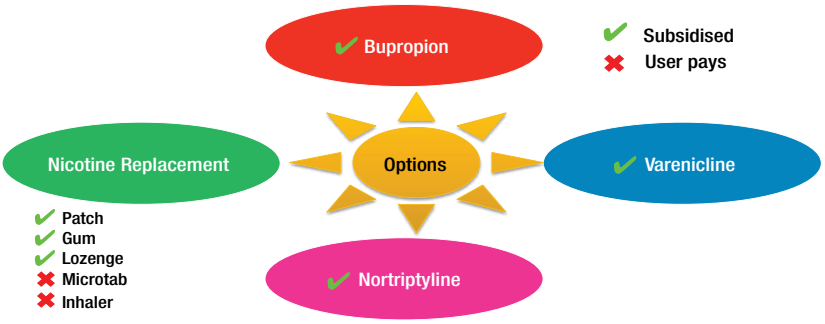
E-cigarettes

Electronic cigarettes (e-cigarettes) have been hugely controversial in New Zealand. They are currently not approved for therapeutic use as a smoking cessation aid. However, in New Zealand changes to the legislation due in 2018 will permit the sale/marketing of e-cigarettes, making them widely available. Evidence from the UK suggests that using e-cigarettes with nicotine is less harmful than smoking tobacco cigarettes, with about 5% of the health risks associated with tobacco cigarettes.[9] The same evidence also suggests that e-cigarettes are not encouraging children or non-smokers to use e-cigarettes because they think it is less harmful than tobacco.[9]

Pharmacotherapy

Pharmacotherapy for smoking cessation in New Zealand includes nicotine replacement therapy in a variety of forms, bupropion, nortriptyline and varenicline (Figure 1).

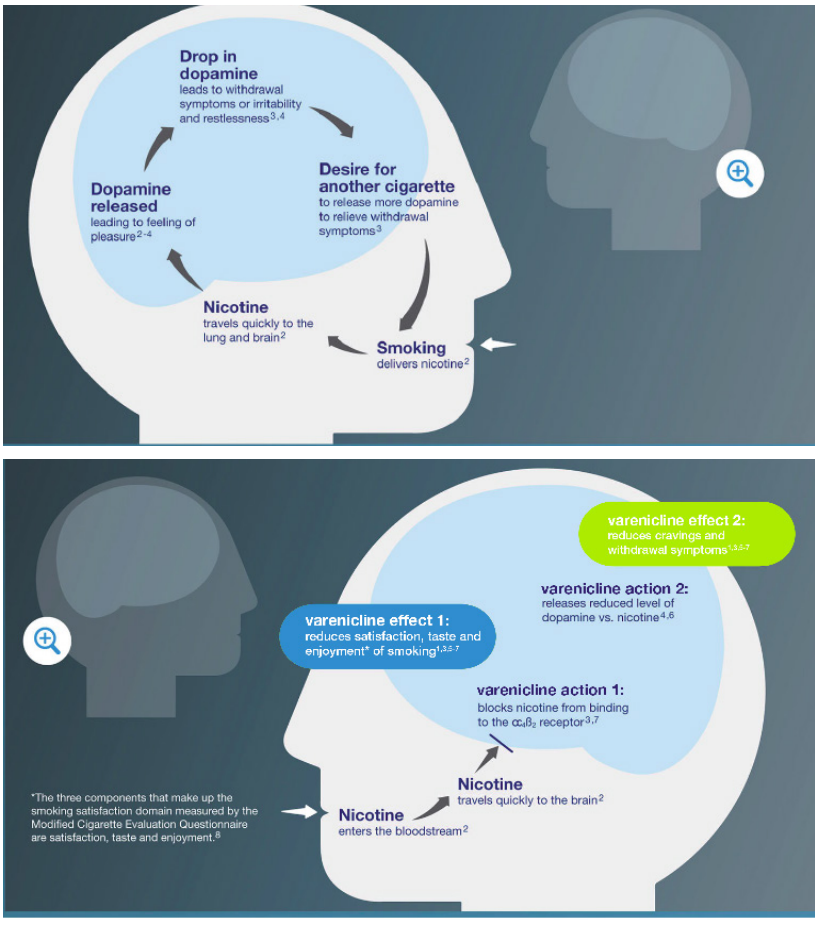
Figure 1. Pharmacotherapy for smoking cessation available in New Zealand



Varenicline for smoking cessation

As shown in Figure 2, nicotine releases dopamine, leading to a feeling of pleasure. A drop in dopamine leads to the desire for another cigarette and so the cycle continues. Varenicline is a partial agonist and antagonist of the nicotine receptor. It binds to the receptor, blocking nicotine, reducing the amount of dopamine released and in doing so reduces the enjoyment of smoking. Varenicline also stimulates the release of a reduced amount of dopamine versus nicotine all the time, thereby reducing cravings and withdrawal symptoms.

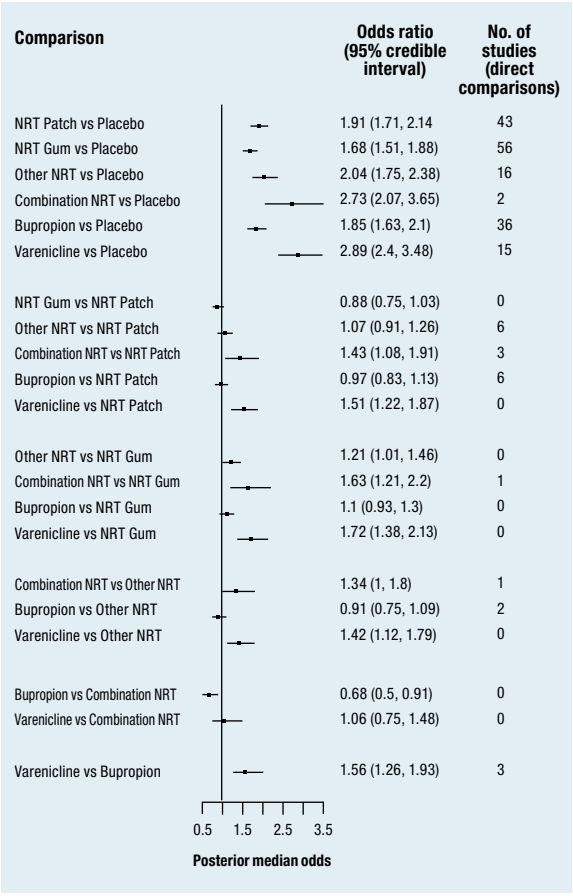
Figure 2. Mechanism of action of nicotine and varenicline



1. Champix (varenicline tartrate) Data Sheet; 2. Dani JA et al, Nat Neurosci 2005; 8: 1465-1470. 3. Zaniewska M et al, Pharmacol Rep 2009; 61: 957-965. 4. Coe JW et al, J Med Chem 2005; 48: 3474 -3477. 5. West R et al, Psychopharmacol 2008; 197: 371 – 377. 6. Gonzales D et al, JAMA 2006; 296: 47-55. 7. Jorenby DE et al, JAMA 2006; 296: 56-63. 8. Cappelleri JC et al, Addict Behav 2007; 32: 912-923.

A 2013 Cochrane network meta-analysis evaluated first-line smoking cessation pharmacotherapies versus placebo and versus each other, with NRT split by type.[10] As shown in Figure 3, varenicline increased the odds of quitting compared with placebo, single forms of NRT and bupropion, but was not more effective than combination NRT.

Figure 3. Network meta-analysis of first-line smoking cessation pharmacotherapies versus placebo and versus each other[10]



Efficacy and safety of varenicline for smoking cessation in patients with mild-to-moderate COPD

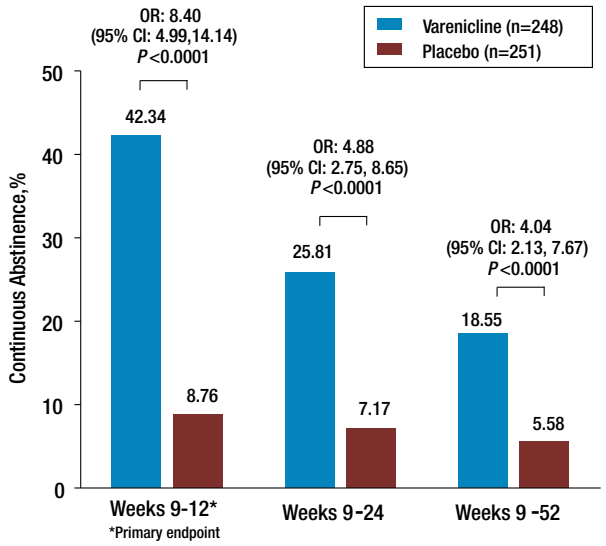
A multicentre, randomised, double-blind, placebo-controlled clinical trial published in *Chest* in 2011 evaluated treatment with varenicline or placebo in patients with mild-to-moderate COPD.[11] Patients (n=504) received 12 weeks of varenicline (1 mg BID, up-titrated during the first week) or placebo and had no known psychiatric history. All patients received brief counselling during study visits. The primary efficacy endpoint was carbon monoxide-confirmed continuous abstinence rate (CAR) for weeks 9–12. A secondary efficacy endpoint was carbon monoxide-confirmed CAR for weeks 9–52.

Efficacy

Patients' mean age was 57 years, they had been smoking for a mean of 40 years, and smoked around one pack a day. The majority of patients had tried to quit previously. CAR for weeks 9 to 12 was significantly higher for patients in the varenicline group than for those in the placebo group (42.34% vs 8.76%; P<0.0001) (Figure 4).

CAR in the patients treated with varenicline remained significantly higher than in those who received placebo through weeks 9 to 52 (18.55% vs 5.58%; P<0.0001). According to Dr Child, it is not surprising that abstinence rates dropped off over the study duration. As in practice it is common for patients to quit, relapse, quit again and relapse again. '*A failure of quitting is not a failure – it is just part of the process, so keep encouraging your patients to try and try again to quit.*' Encouragingly, almost 6% of placebo patients had quit at the end of one year – these were highly motivated patients who knew they were in a study and who had received brief counselling to quit at each visit.

Figure 4. Continuous abstinence rates in patients with COPD taking varenicline vs placebo[11]



Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES)

While the pivotal registration trials established the efficacy and safety of varenicline, case reports of neuropsychiatric adverse events such as suicidal ideation and aggression[12] with varenicline and bupropion arising from post-marketing surveillance led to the issue of a boxed warning by the US Food and Drug Administration (FDA) in the US Prescribing Information.[13] To this end, the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial was initiated as a post-marketing requirement by the US FDA and European Medicines Agency (EMA) for both varenicline and bupropion and was conducted by Pfizer in collaboration with GlaxoSmithKline.[14]

EAGLES was a randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with a 12-week non-treatment follow-up in 16 countries.[14] Subjects were motivated-to-quit smokers with and without a history of or currently stable psychiatric disorders who received brief cessation counselling at each visit. The primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events based on post-marketing reports. It comprised 16 neuropsychiatric symptom categories and captured all volunteered, observed, and solicited neuropsychiatric adverse events in these 16 categories, irrespective of whether the clinician assessed them to be causally related to study medications.

The primary endpoint was met when participants reported at least one event across the 16 symptom categories during treatment or within 30 days of treatment discontinuation. Prespecified severity criteria for the primary neuropsychiatric adverse event endpoint required adverse events for four components expected to be reported more commonly (anxiety, depression, feeling abnormal, or hostility) to be rated as severe. Neuropsychiatric adverse events in the remaining 12 categories (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, behaviour, or completed suicide) met severity criteria when rated as either moderate or severe. The main efficacy endpoint was biochemically confirmed CAR for weeks 9-12.

Safety

8144 subjects were randomly assigned, 4116 to the psychiatric cohort (4074 included in the safety analysis) and 4028 to the non-psychiatric cohort (3984 included in the safety analysis). The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo (Table 1). There were more neuropsychiatric adverse events in the psychiatric cohort overall (5.8%) than the non-psychiatric cohort (2.1%; P<0.0001), regardless of treatment. During treatment in the non-psychiatric cohort, one NRT subject attempted suicide and one placebo subject completed suicide.

The average total HADS score improved from baseline through the treatment phase by about 2 points in the non-psychiatric cohort and 3 points in the psychiatric cohort, an effect that was similar across the treatment groups.

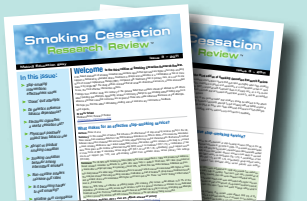
Across cohorts, the most frequently reported adverse events were nausea (varenicline 25.3%; bupropion 10.0%; NRT 9.8%; placebo 6.8%), headache (varenicline 12.2%; bupropion 9.3%; NRT 11.5%; placebo 9.9%), abnormal dreams (varenicline 10.0%; bupropion 6.6%; NRT 12.4%; placebo 4.6%) and insomnia (varenicline 9.4%; bupropion 12.2%; NRT 9.6%; placebo 6.9%).

Table 1. Neuropsychiatric adverse events composite endpoint in subjects receiving varenicline, bupropion, NRT or placebo in the EAGLES study[14]

Cohort	Number (percentage) of subjects with ≥1 events (n/N, %)			
	Varenicline	Bupropion	NRT	Placebo
Non-Psychiatric	13/990 **1.3%**	22/989 **2.2%**	25/1006 **2.5%**	24/999 **2.4%**
Psychiatric	67/1026 **6.5%**	68/1017 **6.7%**	53/1016* **5.2%**	50/1015 **4.9%**
Overall (both cohorts)	80/2016 **4.0%**	90/2006 **4.5%**	78/2022 **3.9%**	74/2014 **3.7%**

AEs reported during treatment and ≤30 days after last dose.

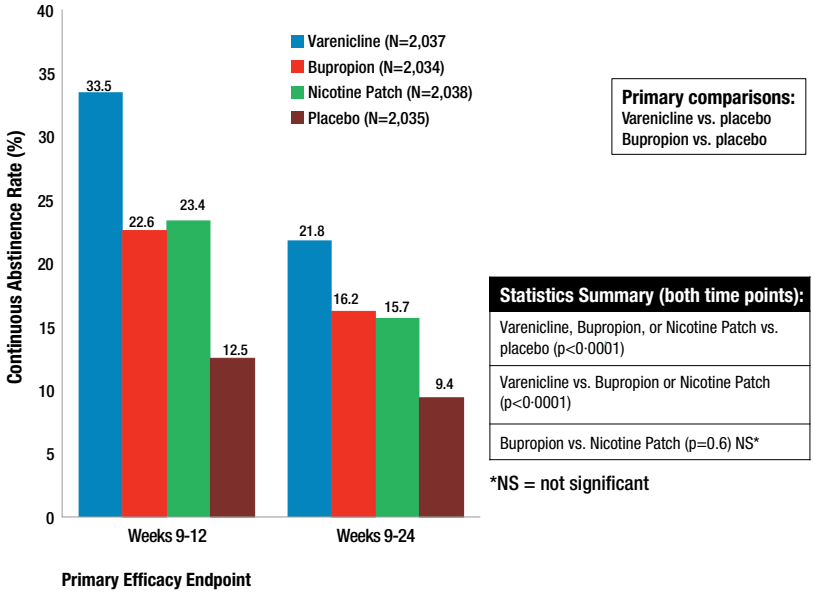
* One additional participant (Psychiatric/NRT group) who reported moderate suicidal ideation was identified after clinical database lock and was not included in the analysis.



Efficacy

CAR for varenicline, bupropion and NRT at weeks 9-12 and weeks 9-24 were significantly higher compared to placebo, and CAR for varenicline at both time points were significantly higher compared to bupropion and NRT (Figure 5).

Figure 5. Continuous abstinence rates in subjects receiving varenicline, bupropion, NRT or placebo in the EAGLES study[14]



Discussion

At the conclusion of the study, the data showed that there was no significant increase in the rate of neuropsychiatric adverse events with either varenicline or bupropion relative to nicotine patch or placebo in either cohort. The overall incidence in each group was varenicline 4%, bupropion 4.5%, nicotine patch 3.9%, and placebo 3.7%. The study detected about a 4% significant difference in the rate of neuropsychiatric adverse events between the psychiatric and non-psychiatric cohorts (5.8% vs 2.1%; p<0.0001), although there were no significant differences between individual groups. The results from this study led the FDA to remove the boxed warning from each product's labelling. However, a number of concerns have been raised about the study. The first is that the EAGLES study was not powered to detect rare neuropsychiatric adverse events (e.g. suicidal ideation/behaviour) and the potential for these events should not be overlooked. A second point is that the study used a composite endpoint that has not been validated in any other trials, while a third point is that, rather than employing standard rating scales, clinicians themselves rated the severity of adverse events. Critics have argued that the boxed warning should not be removed from the label by the FDA. It is important to remember that doctors should advise patients attempting to quit smoking with varenicline of the possible emergence of neuropsychiatric symptoms, including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour. Patients and their families should be advised that the patient should stop taking varenicline and contact a healthcare professional immediately if such symptoms are observed. Regardless, from an efficacy point of view, the EAGLES study demonstrated superiority with varenicline when compared to bupropion, NRT patch and placebo.

CONCLUDING COMMENTS: DR CHILD

- COPD is the fourth leading cause of death in New Zealand.
- Smoking is the most important risk factor for COPD.
- Smoking cessation is an important tool in prevention for patients at all stages of COPD.
- Smoking cessation pharmacotherapy available in New Zealand includes NRT in various forms, bupropion, nortriptyline and varenicline.
- Health professionals are the key – the first step is to ask every single smoker if they want help to quit.

REFERENCES

1. Ministry of Health. 2017. Annual Data Explorer 2016/17: New Zealand Health Survey [Data File]. URL: https://minhealthnz.shinyapps.io/nz-health-survey-2016-17-annual-update.
2. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391-8.
3. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681-6.
4. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org.
5. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365(13):1184-92.
6. Wright, C. (2008). Excess Costs to Health Care as a Result of Tobacco Use in New Zealand During 2006/2007. Ministry of Health, Wellington, NZ.
7. Ministry of Health. 2010. Tobacco Use in New Zealand: Key findings from the 2009 New Zealand Tobacco Use Survey. Wellington: Ministry of Health.
8. Ministry of Health. 2014. The New Zealand Guidelines for Helping People to Stop Smoking. Wellington: Ministry of Health.
9. McNeill A, Brose LS, Calder R, et al. E-cigarettes: an evidence update. A report commissioned by Public Health England. 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf
10. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;(5):CD009329.
11. 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(3):591-599.
12. Institute for Safe Medication Practices. Quarter watch: monitoring FDA MedWatch reports. Sept 24, 2014. Data from 2013 Quarters 2 and 3. 2014. http://www.ismp.org/quarterwatch/pdfs/2013Q3.pdf.
13. US Food and Drug Administration. FDA drug safety newsletter, volume 2, number 1, 2009. 2009. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm107311.htm.
14. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet. 2016;387(10037):2507-20.

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