

Review Article

Varenicline

A Novel Pharmacotherapy for Smoking Cessation

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Supplementary Material

This supplementary material contains the table referred to in the full version of this article, which can be found at <http://drugs.adisonline.com>.

^aTreatment was for 12 weeks except where otherwise indicated. Each row lists the incidence of adverse events reported in the primary publication for that study. A blank cell indicates no adverse event was reported under that terminology in the publication.

^bThe incidence of an adverse event was reported if $\geq 5\%$ in the varenicline group and more frequent than in the placebo group.

^cThe incidence of an adverse event was reported if $\geq 5\%$ in either the varenicline or bupropion SR group and more frequent than in the placebo group.

^dThe incidence of an adverse event was reported if $\geq 5\%$ in any treatment group.

^eThe incidence of an adverse event in the open-label study was reported if $\geq 5\%$. In the double-blind extension, the incidence of an adverse event was reported if $\geq 5\%$ in the varenicline group and more frequent in the varenicline group than the placebo group.

^fThe incidence of an adverse event was reported if $\geq 10\%$ in any treatment group, including placebo.

bid = twice daily; **Bupropion SR** = sustained-release bupropion; **qd** = once daily

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006 Nov; 3(11): e442
2. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004 Jun 26; 328(7455): 1519
3. Shearer J, Shanahan M. Cost effectiveness analysis of smoking cessation interventions. *Aust N Z J Public Health* 2006 Oct; 30(5): 428-34
4. Warner KE. Cost effectiveness of smoking-cessation therapies. Interpretation of the evidence and implications for coverage. *Pharmacoeconomics* 1997 Jun; 11(6): 538-49
5. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007 Jan 24; (1): CD000031
6. Stead L, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008 Jan 23; (1): CD000146
7. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2007 Jan 24; (1): CD006103
8. US Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the Surgeon General. Rockville, MD; 1988
9. Jarvis MJ. Why people smoke. *BMJ* 2004 Jan 31; 328(7434): 277-9
10. Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur J Pharmacol* 2000 Mar 30; 393(1-3): 295-314
11. Maskos U, Molles BE, Pons S, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. *Nature* 2005 Jul 7; 436(7047): 103-7
12. Tapper AR, McKinney SL, Nashmi R, et al. Nicotine activation of $\alpha 4^*$ receptors: sufficient for reward, tolerance, and sensitization. *Science* 2004 Nov 5; 306(5698): 1029-32
13. Picciotto MR, Zoli M, Rimondini R, et al. Acetylcholine receptors containing the $\beta 2$ subunit are involved in the reinforcing properties of nicotine. *Nature* 1998 Jan 8; 391(6663): 173-7
14. Whiting PJ, Lindstrom JM. Characterization of bovine and human neuronal nicotinic acetylcholine receptors using monoclonal antibodies. *J Neurosci* 1988 Sep; 8(9): 3395-404
15. Corringer PJ, Le Novère N, Changeux JP. Nicotinic receptors at the amino acid level. *Annu Rev Pharmacol Toxicol* 2000; 40: 431-58
16. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an $\alpha 4\beta 2$ nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005 May 19; 48(10): 3474-7
17. Tutka P, Zatonski W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. *Pharmacol Rep* 2006 Nov-Dec; 58(6): 777-98
18. Etter JF. Cytisine for smoking cessation: a literature review and a meta-analysis. *Archives of internal medicine* 2006 Aug 14-28; 166(15): 1553-9
19. Pfizer Inc. Chantix (varenicline tartrate) US prescribing information. January, 2008 Available from: http://www.chantix.com/content/Prescribing_Information.jsp [Accessed 2008 Nov 4]

20. Rollema H, Chambers LK, Coe JW, et al. Pharmacological profile of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. *Neuropharmacology* 2007 Mar; 52(3): 985-94
21. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Mol Pharmacol* 2006 Sep; 70(3): 801-5
22. Obach RS, Reed-Hagen AE, Krueger SS, et al. Metabolism and disposition of varenicline, a selective $\alpha 4\beta 2$ acetylcholine receptor partial agonist, in vivo and in vitro. *Drug Metab Dispos* 2006 Jan; 34(1): 121-30
23. Faessel HM, Gibbs MA, Clark DJ, et al. Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. *Journal of clinical pharmacology* 2006 Dec; 46(12): 1439-48
24. Burstein AH, Fullerton T, Clark DJ, et al. Pharmacokinetics, safety, and tolerability after single and multiple oral doses of varenicline in elderly smokers. *J Clin Pharmacol* 2006 Nov; 46(11): 1234-40
25. Xiao Y, Lv Y, Zhang X, Guo Y, Bergstrom T. The pharmacokinetic and tolerability profile of varenicline in healthy Chinese volunteers *J Clin Pharmacol* 2008; In press:
26. Pfizer Inc. Chantix (varenicline tartrate) European prescribing information. April 2008 Available from: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/champix/H-699-PI-en.pdf> [Accessed 2008 Nov 4]
27. Faessel HM, Smith BJ, Gibbs MA, et al. Single-dose pharmacokinetics of varenicline, a selective nicotinic receptor partial agonist, in healthy smokers and nonsmokers. *Journal of clinical pharmacology* 2006 Sep; 46(9): 991-8
28. Feng B, Obach RS, Burstein AH, et al. Effect of human renal cationic transporter inhibition on the pharmacokinetics of varenicline, a new therapy for smoking cessation: an in vitro-in vivo study. *Clin Pharmacol Ther* 2008 Apr; 83(4): 567-76
29. Burstein AH, Clark DJ, O'Gorman M, et al. Lack of pharmacokinetic and pharmacodynamic interactions between a smoking cessation therapy, varenicline, and warfarin: an in vivo and in vitro study. *J Clin Pharmacol* 2007 Nov; 47(11): 1421-9
30. Faessel HM, Burstein AH, Troutman MD, et al. Lack of a pharmacokinetic interaction between a new smoking cessation therapy, varenicline, and digoxin in adult smokers. *Eur J Clin Pharmacol* 2008 Nov; 64(11): 1101-9
31. Hughes JR, Benowitz N, Hatsukami D, et al. Clarification of SRNT workgroup guidelines for measures in clinical trials of smoking cessation therapies. *Nicotine Tob Res* 2004 Oct; 6(5): 863-4
32. Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective $\alpha 4\beta 2$ nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Archives of internal medicine* 2006 Aug 14-28; 166(15): 1561-8
33. 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 Aug 14-28; 166(15): 1571-7
34. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006 Jul 5; 296(1): 47-55
35. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006 Jul 5; 296(1): 56-63
36. Tonstad S, Tønnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006 Jul 5; 296(1): 64-71
37. 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 Aug; 63(8): 717-24

38. Tsai ST, Cho HJ, Cheng HS, et al. A randomized, placebo-controlled trial of varenicline, a selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther* 2007 Jun; 29(6): 1027-39
39. Nakamura M, Oshima A, Fujimoto Y, et al. Efficacy and tolerability of varenicline, an $\alpha 4\beta 2$ 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 Jun; 29(6): 1040-56
40. Wang C, Xiao D, Chan KP, et al. Varenicline for smoking cessation: Efficacy and tolerability in a placebo-controlled, randomized study in smokers from China, Singapore and Thailand. *Respirology* 2008; In press:
41. Fiore MC. US public health service clinical practice guideline: treating tobacco use and dependence. *Respir Care* 2000 Oct; 45(10): 1200-62
42. Nides M, Glover ED, Reus VI, et al. Varenicline versus bupropion SR or placebo for smoking cessation: a pooled analysis. *Am J Health Behav* 2008 Nov-Dec; 32(6): 664-75
43. Niaura R, Hays JT, Jorenby DE, et al. The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. *Curr Med Res Opin* 2008 Jul; 24(7): 1931-41
44. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986 Mar; 43(3): 289-94
45. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 2001 Feb; 3(1): 7-16
46. Cappelleri JC, Bushmakina AG, Baker CL, et al. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. *Addict Behav* 2007 May; 32(5): 912-23
47. West R, Baker CL, Cappelleri JC, et al. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology (Berl)* 2008 Apr; 197(3): 371-7
48. Patterson F, Jepsen C, Strasser AA, et al. Varenicline improves mood and cognition during smoking abstinence. *Biol Psychiatry* 2009, Jan; 65(2): 144-149
49. Williams KE, Reeves KR, Billing CB, Jr., et al. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. *Curr Med Res Opin* 2007 Apr; 23(4): 793-801
50. Parsons AC, Shraim M, Inglis J, et al. Interventions for preventing weight gain after smoking cessation. *Cochrane database of systematic reviews (Online)* 2009; (1): CD006219
51. United States Food and Drug Administration. Information for Healthcare Professionals: Varenicline (marketed as Chantix). Available from: <http://www.fda.gov/cder/drug/InfoSheets/HCP/vareniclineHCP.htm> [Accessed 2008 Nov 4]
52. Cahill K, Stead L, Lancaster T. A preliminary benefit-risk assessment of varenicline in smoking cessation. *Drug Saf* 2009; 32(2): 119-35
53. Pfizer Inc. Medication Guide Chantix® (varenicline) Tablets. May 2008 Available from: http://www.pfizer.com/files/products/ppi_chantix.pdf [Accessed 2009 March 26]
54. 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 Jan; 103(1): 146-54
55. McClure JB, Swan GE, Jack L, et al. Mood, Side-effects and Smoking Outcomes Among Persons With and Without Probable Lifetime Depression Taking Varenicline. *Journal of General Internal Medicine* 2009 Feb 24: Epub ahead of print

56. Evins AE, Goff DC. Varenicline treatment for smokers with schizophrenia: a case series. *J Clin Psychiatry* 2008 Jun; 69(6): 1016
57. McColl SL, Burstein AH, Reeves KR, et al. Human abuse liability of the smoking cessation drug varenicline in smokers and nonsmokers. *Clin Pharmacol Ther* 2008 Apr; 83(4): 607-14
58. Freedman R. Exacerbation of schizophrenia by varenicline. *Am J Psychiatry* 2007 Aug; 164(8): 1269
59. Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. *Am J Psychiatry* 2007 Aug; 164(8): 1269-70
60. Popkin MK. Exacerbation of recurrent depression as a result of treatment with varenicline. *Am J Psychiatry* 2008 Jun; 165(6): 774
61. Pirmoradi P, Roshan S, Nadeem SS. Neuropsychiatric disturbance after initiation of varenicline in a patient with a history of alcohol abuse and major depression. *Am J Health Syst Pharm* 2008 Sep 1; 65(17): 1624-6
62. Pumariega AJ, Nelson R, Rotenberg L. Varenicline-induced mixed mood and psychotic episode in a patient with a past history of depression. *CNS Spectr* 2008 Jun; 13(6): 511-4
63. Moore TJ, Cohen MR, Furberg CD. Strong safety signal seen for new varenicline risks. May 21, 2008 Available from: <http://www.ismp.org/docs/vareniclineStudy.asp> [Accessed 2008 Nov 4]
64. Hauben M, Wilson G, Reich L. A preliminary quantitative analysis of the spontaneous reporting of selected adverse events with chantix in the US FDA adverse event reporting system data base. 10th Annual Conference of SRNT Europe; 2008 23-26 September Rome, Italy
65. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1995