A summary of the Cochrane review:

Nicotine receptor partial agonists for smoking cessation

Kate Cahill[1], Nicola Lindson-Hawley[1], Kyla Thomas[2], Thomas R Fanshawe[1], Tim Lancaster[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

[2]School of Social and Community Medicine, University of Bristol, Bristol, UK

Can nicotine receptor partial agonists, including cytisine and varenicline, help people to stop smoking?

Background

Nicotine receptor partial agonists aim to reduce the withdrawal symptoms people feel when they stop smoking and the pleasure people usually experience when they smoke. The most widely-available treatment in this drug type is varenicline, which is available world-wide as an aid for quitting smoking. Cytisine is a similar medication, but is only available in Central and Eastern European countries and through internet sales.

Study characteristics

We found 39 studies of varenicline compared to placebo, bupropion or nicotine patches. We also found 4 trials of cytisine, 1 of which compared it to nicotine replacement therapy. We include 1 trial of dianicline, which is no longer in development, and so not available to use. To be included, trials had to report quit rates at least 6 months from the start of treatment. We preferred the strictest available definition of quitting, and results which had been biochemically confirmed by testing blood or bodily fluids. We conducted full searches up to May 2015, although we have also included several key trials published after that date.

Key results

We found 27 trials with 12,625 people investigating varenicline at standard dose, which more than doubled the chances of quitting compared with placebo. Low-dose varenicline (4 trials, 1266 people) roughly doubled the chances of quitting, and reduced the number and severity of side effects. The number of people stopping smoking with varenicline was higher than with bupropion (5 trials, 5877 people) or with NRT (8 trials, 6264 people). Varenicline delivers one extra successful quitter for every 11 people treated, compared with smokers trying to quit without varenicline.

The most common side effect of varenicline is nausea, but this is mostly at mild or moderate levels and usually clears over time. People taking varenicline appear to have about a 25% increased chance of a serious adverse event, although these include many unrelated to treatment. Also, more people were lost from the control groups than from the varenicline groups by the end of the trials, which may mean that the event counts in the control groups is lower than it should be. After varenicline became available to use, there were concerns that it could be linked with an increase in depressed mood, agitation, or suicidal thinking and behaviour. However, the

latest evidence does not support a link between varenicline and these disorders, although people with past or current psychiatric illness may be at slightly higher risk. There have also been concerns that varenicline may slightly increase heart and circulatory problems in people already at increased risk of these illnesses. The evidence is currently unclear whether or not they are caused or made worse by varenicline, but we should have clearer answers to these questions when a further study is published later in 2016.

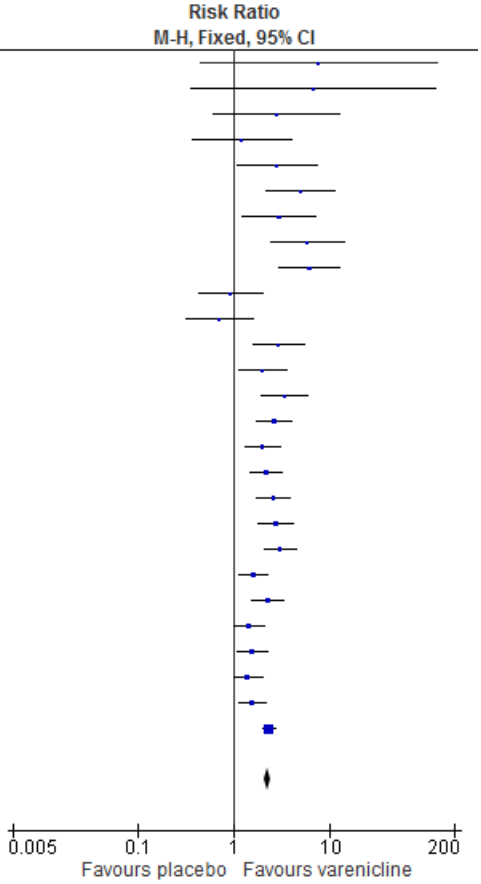
Quality of the evidence

Varenicline studies were generally of high quality, providing evidence we consider reliable and robust. We rate the quality of the evidence comparing varenicline with NRT as moderate quality (reasonably confident of the stability), since in some of them the participants knew which treatment they were receiving (i.e. non-blinded trials). Evidence from the cytisine trials is judged low quality (limited confidence), as there are only 2 trials, with few participants.

A forest plot illustrating the effect of standard dose varenicline versus placebo on quitting smoking at longest follow-up (≥ 6 months)

Study or Subgroup	Varenicline Events	Varenicline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Dios 2012 (1)	3	10	0	11	0.1%	7.64 [0.44, 131.75]
Nahvi 2014a (2)	3	57	0	55	0.1%	6.76 [0.36, 127.89]
Chengappa 2014	6	31	2	29	0.3%	2.81 [0.61, 12.81]
Westergaard 2015 (3)	5	26	4	25	0.6%	1.20 [0.36, 3.97]
Evins 2014	12	40	5	47	0.7%	2.82 [1.09, 7.32]
Heydari 2012 (4)	29	89	6	91	0.9%	4.94 [2.16, 11.32]
Nides 2006	18	125	6	123	0.9%	2.95 [1.21, 7.19]
Oncken 2006	58	259	5	129	1.0%	5.78 [2.38, 14.05]
Gonzales 2014	50	249	8	245	1.2%	6.15 [2.98, 12.70]
NCT00828113	10	50	11	51	1.6%	0.93 [0.43, 1.99]
Steinberg 2011 (5)	8	40	11	39	1.6%	0.71 [0.32, 1.57]
Niaura 2008	35	160	12	160	1.7%	2.92 [1.57, 5.41]
Cinciripini 2013	24	86	15	106	2.0%	1.97 [1.11, 3.52]
Tashkin 2011	46	248	14	253	2.0%	3.35 [1.89, 5.94]
Rigotti 2010	68	353	26	354	3.8%	2.62 [1.71, 4.02]
Anthenelli 2013	52	254	28	269	3.9%	1.97 [1.28, 3.01]
Tsai 2007	59	126	27	124	3.9%	2.15 [1.47, 3.15]
Gonzales 2006	77	352	29	344	4.3%	2.59 [1.74, 3.87]
Rennard 2012	171	493	21	166	4.6%	2.74 [1.81, 4.16]
Bolliger 2011	155	394	26	199	5.0%	3.01 [2.06, 4.40]
Nakamura 2007	56	155	35	154	5.1%	1.59 [1.11, 2.28]
Jorenby 2006	79	344	35	341	5.1%	2.24 [1.55, 3.24]
Wong 2012 (6)	55	151	34	135	5.2%	1.45 [1.01, 2.07]
Carson 2014 (7)	56	190	36	189	5.2%	1.55 [1.07, 2.23]
Eisenberg 2016	53	148	39	151	5.6%	1.39 [0.98, 1.96]
Wang 2009	63	165	42	168	6.0%	1.53 [1.10, 2.12]
EAGLES 2016 (8)	444	2037	191	2035	27.7%	2.32 [1.98, 2.72]
Total (95% CI)		**6632**		**5993**	**100.0%**	**2.24 [2.06, 2.43]**
Total events	1695		668			

Heterogeneity: Chi² = 64.85, df = 26 (P < 0.0001); I² = 60%
Test for overall effect: Z = 19.01 (P < 0.00001)



Footnotes
(1) 7-day PPA at 6m
(2) 7-day PPA at 24 wks
(3) PPA at 24 wks
(4) PPA at 12m
(5) 7-day PPA at 24 weeks
(6) 7-day PPA at 12m
(7) 24-month follow-up
(8) Extrapolated from % reported quit

Citation:
Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub7.

Online at:
http://onlinelibrary.wiley.com/wol1/doi/10.1002/14651858.CD006103.pub7/abstract